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LESION IN PERIPHERAL NERVE RESULTING FROM COMPRESSION BY SPRING CLIP

D. DENNY-BROWN, M.B., AND CHARLES BRENNER, M.D.
BOSTON

The retention of faradic excitability by a nerve or nerve branch peripheral to a lesion which blocks conduction from above is an unusual phenomenon, first described by Erb[1] (1876). Sensation is then slightly, if at all, affected. This phenomenon is usually encountered when nerve has been subjected to a relatively brief period of severe compression, as in cases of the radial or peroneal palsy resulting from some posture in sleep or in intoxication (Dejerine and Bernheim[2] 1899). The cases of milder paralysis produced by a tourniquet also have this characteristic, and in a previous paper (Denny-Brown and Brenner[3]) we made an experimental analysis of some of the factors involved in the production of the lesion and of the associated histologic changes produced by a tourniquet. The "paradoxic" electrical reaction of Erb has been reported in association with neuroma and extraneural scar tissue (Platt,[4] Frazier and Silbert,[5] Kraus and Ingham,[6]), particularly the lesions resulting from war wounds. In the present investigation we attempt to analyze the factors concerned in the production of the lesion by prolonged direct compression to the nerve.

In our first paper we described experiments on the sciatic nerve of the cat in which we sought to ascertain the relation between the degree of pressure applied to a short segment of the nerve and the resulting disorder of function. The relation was, however, purely relative and, when measured by the latency before onset of paralysis, was subject to wide variation, owing to the escape of small vessels in the epineurium from the full pressure applied. This variability was present both when pressure was directly applied to the nerve and when it was indirectly produced by a tourniquet applied to the surface of the limp. It has been shown by Grundfest[7] that oxygenated frog nerve can withstand enormous pressures (15,000 pounds per square inch [6,804 Kg. per 6.45 cm.]) without impairment of conduction. The damaging effect of such pressures as we used may therefore be related to occlusion of the blood vessels of the nerve. Moreover, the increasingly shorter latency of failure in mammalian nerve with increasing pressures (of the order of 20 to 100 cm. of mercury) is considered to be due to increasing degrees of relative ischemia.

We had found that two hours of continuous application to the surface of the skin of a tourniquet resisting the passage of mercury at a pressure of 70 cm. of mercury was required in order to induce a paralysis lasting more than twenty-four hours. The paralysis thus caused shows interesting features. It appears to affect sensation little, if at all, as far as can be judged from animal experiments. The electrical excitability of the nerve and muscle below the lesion persists until recovery occurs (Erb's paradoxic phenomenon). Recovery of motor conduction began in most cases between the fifth and the nineteenth

From the Neurological Unit, Boston City Hospital and the Department of Neurology, Harvard Medical School.

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day and was rapid and complete. The muscle did not fibrillate. Greater pressure or longer duration of application resulted in our experiments in more severe damage to the nerve, with all the phenomena of a degenerative lesion of nerve.

The histologic features of the transient "intermediate type of paralysis from pressure" produced by application of a tourniquet revealed that there was an alteration of the myelin sheath at the site of compression. This began with widening of the nodes of Ranvier, and with a more severe degree of compression long segments of axis-cylinder with thinning or absence of myelin alternated with stretches of the cylinder coated with granular myelin. The axis-cylinder lost its argentophilic property where the myelin was defective and either appeared as a fine thread or was unstainable by silver methods. In certain circumstances this bared portion of axon stained selectively by the iron hematoxylin method. The mesoblastic tissues showed reactionary edema, with lymphocytic infiltration and proliferation of the endoneurium.

The histologic lesion produced by compression with a tourniquet is free from changes secondary to exposure of the nerve. The possibility of any acute flexion or deformity at the point of compression is minimized. The method, however, does not enable any exact identification of the region subjected to pressure. Further, since one of the objectives of the study was to determine the manner in which constricting bands of scar tissue disturb neural function, a more direct imitation of the action of such a directly constricting band was desirable.

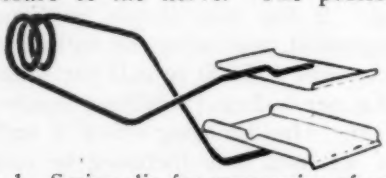

Fig. 1.—Spring clip for compression of nerve.

METHOD

The experiments were performed on cats under anesthesia induced with pentobarbital sodium. The sciatic nerve was exposed with sterile precautions, and a light spring clip, of a pattern shown in figure 1, was applied to the nerve. The clip consisted of a few turns of brass or steel wire, the ends of which were soldered to two small brass plates, 7 mm. by 11 mm., in such a way that the spring could lie parallel to the nerve, which was held between the plates. Each plate had a slight curvature to lessen the chance of its slipping from the nerve. In later experiments the lateral edges of one plate were bent sharply to form a trough into which the other plate fitted. The distal and proximal edges of each plate were everted to avoid any cutting or sharp angulation of the nerve.

A series of such clips were made in a range of spring tensions. The calibration of the compression effect of each clip was determined both by its ability to obstruct the flow of mercury in a thin-walled rubber tube held by the clip and by the tension, expressed in grams, required just to separate the blades. The widening of the clip by the passage of mercury involves friction and requires more pressure than is needed to keep it open at the lower tensions. We, therefore, were more confident of accurate calibration in terms of the weight required to separate the plates. The experiments were of two types—either the application of a strong clip for two hours and subsequent observation for periods up to eight weeks, or continuous application of a weak clip for varying periods up to eight weeks.

The nerve was always exposed, with the animal under anesthesia induced with pentobarbital sodium, and stimulated electrically above and below the clip before the animal was killed. The nerve was then fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. in saline solution and either stained with osmic acid and sectioned in paraffin or embedded in pyroxylin and stained by the Gros-Bielschowsky, the Nissl or the iron hematoxylin method.

In order to control the regenerative effects inherent in a study of the lesion at an interval after production of the lesion, the sciatic nerve opposite that chosen for pressure was usually clamped in a hemostat for ten seconds, a complete lesion being thus produced. On the clamped side there were complete paralysis of spreading of the toes, plantar and dorsiflexion at the ankle and loss of sensation in the foot.

EFFECT OF PRESSURE FOR TWO HOURS

As was observed in short experiments with a mercury bag previously reported, the results of application of clips of various tensions for two hours showed some variation in the severity and the latency of onset of the effect of any one clip in different animals. Thus, in 1 experiment the application of a 100 Gm. clip to one sciatic nerve (motor conduction failed in thirty-three minutes) and of a 200 Gm. clip to the other (motor conduction failed in thirty minutes), each left in place for two hours, was not followed by any sign of paralysis and weakness. When the animal was killed fourteen days later, there was no defect in conduction. The previously compressed segment of nerve was slightly swollen. In histologic sections this region of the nerve was edematous, with occasional lymphocytes scattered through the bundles. The myelin sheaths were here slightly increased in diameter, and the axis-cylinders in Bielschowsky preparations showed great thickening in the affected region. The myelin was pale on either side of each node of Ranvier, and in a few fibers it was in partial dissolution in this situation. No degeneration had occurred. The nerve above and below this area was of normal structure. In another experiment with the same clips (failure of conduction at forty-four and forty-seven minutes respectively) there was no defect after twenty-four hours except that the toes did not spread on either side. Spreading reappeared by the twelfth day.

On the thirteenth day the nerve was exposed, with the animal under light anesthesia, and stimulated directly; no defect in conduction was noted. Histologic examination revealed edema, with complete dissolution of myelin for 0.1 mm. at some of the nodes of Ranvier in a few of the sheaths in the compressed region, and swelling and vacuolation of the axis-cylinders throughout the same region in silver impregnation preparations (fig. 2 *A*). The Schwann cells did not appear changed, though lymphocytes and macrophages were present in small numbers.

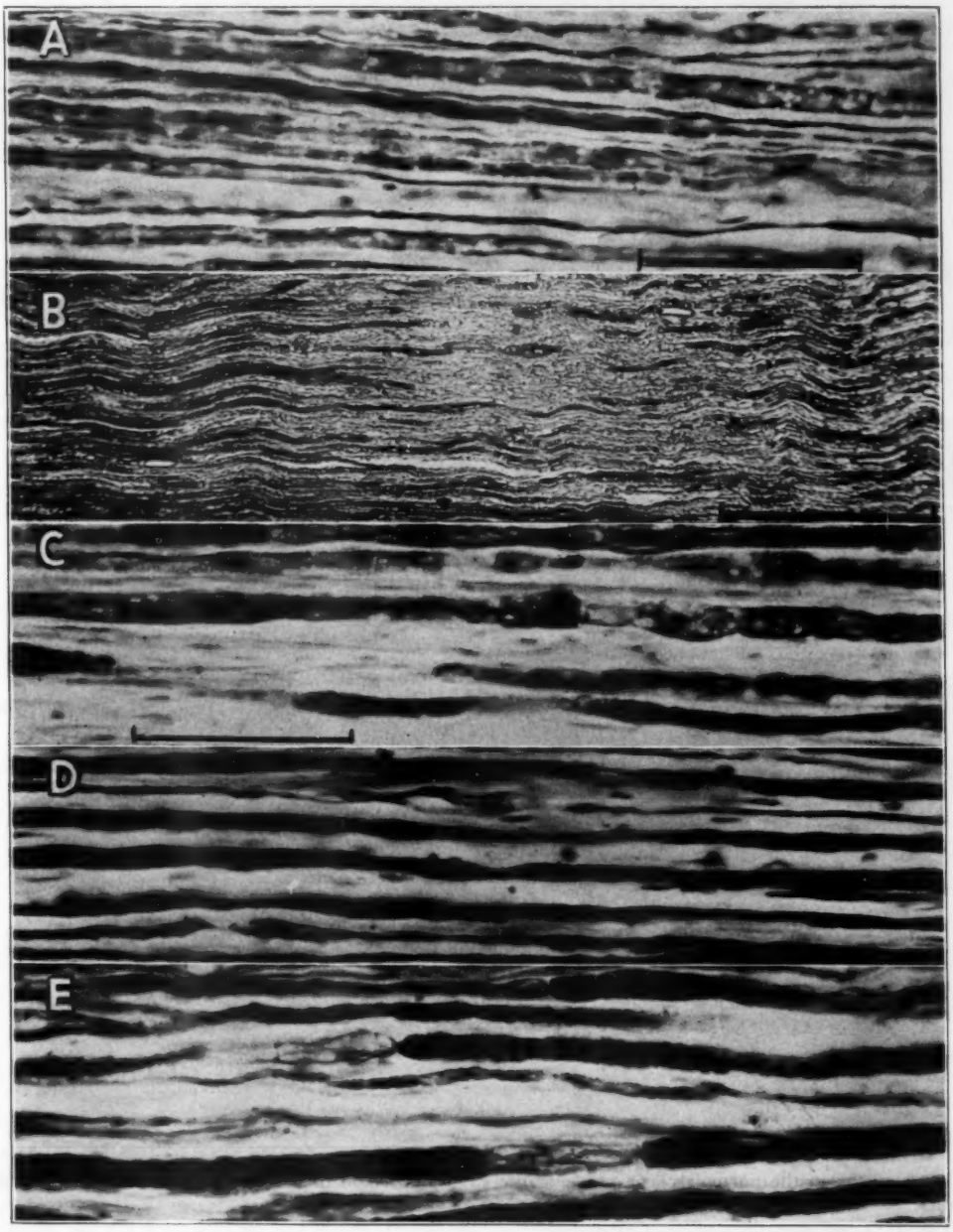

Fig. 2.—*A*, edematous swelling of axis-cylinders two weeks after compression by a 200 Gm. clip for two hours, with no defect in conduction. The measured line is equivalent to 0.1 mm. Gros-Bielschowsky method.

B, demyelination nine days after compression for two hours, with production of paralysis. The distal segment is to the right. The measured line is equivalent to 0.5mm. Osmic acid strain.

C, demyelination fifty-five days after application of heavy clip for two hours, causing paralysis, which began to clear on the twentieth day. There was no block at the end of the experiment. The measured line in *C* and *D* is equivalent to 0.1 mm. Osmic acid stain.

D, axis-cylinders fifty-five days after compression, showing nodes at the level of the previous compression. Gros-Bielschowsky method.

E, a section similar to that in *C*, showing nodes. Osmic acid stain.

A 170 Gm. clip, which caused failure of conduction in forty minutes, when left on for two hours in all, caused complete motor paralysis for five days. Four days later the nerve was examined, and a myelin stain showed loss of myelin sheaths for 4 mm. (fig. 2 *B*). The myelin peripheral to the lesion was normal in all respects.

in the ensuing three to seven days, a small amount of stationary weakness being left for as long as seven weeks. In 1 experiment it was ascertained that the pretibial muscles remained excitable to a percutaneous faradic stimulus throughout a period of complete paralysis of eighteeen days. At the time the animals were killed, after

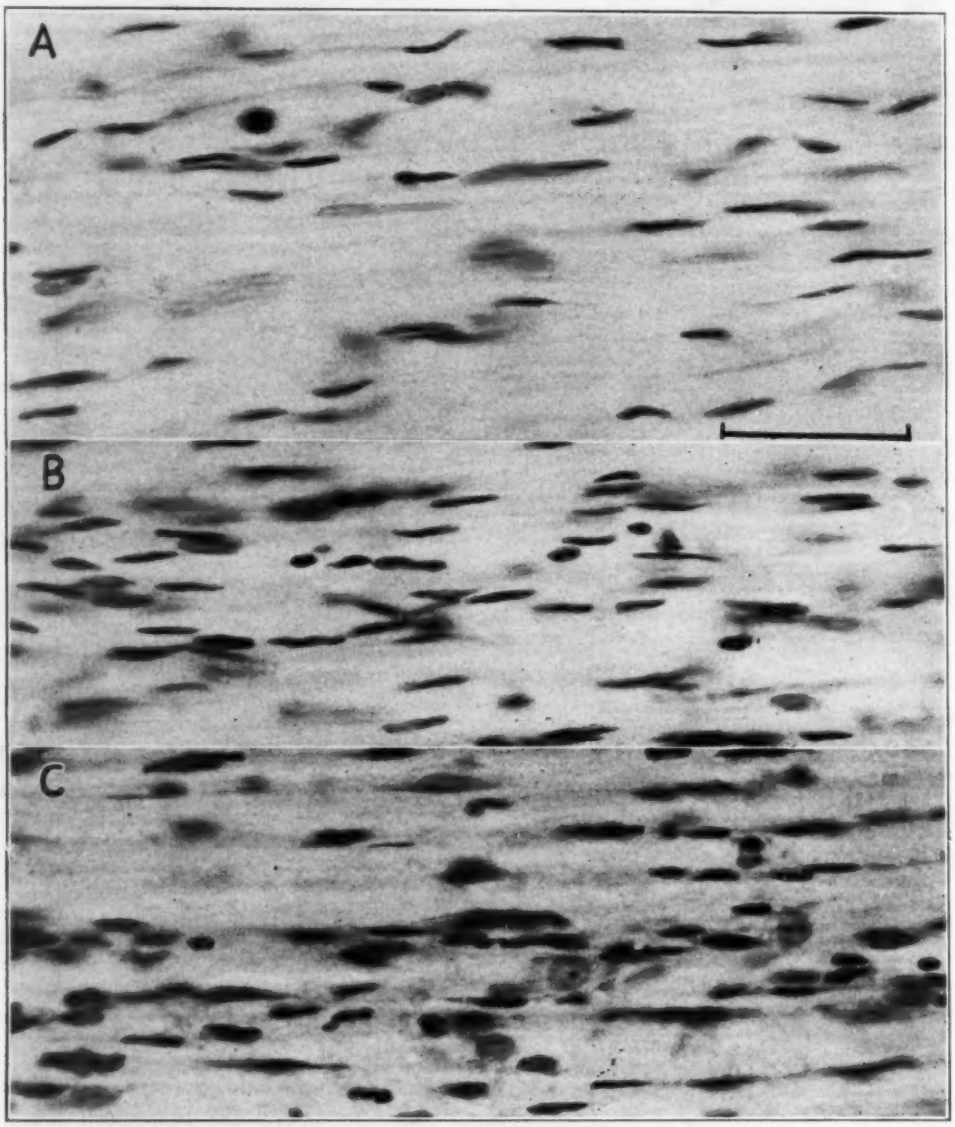

Fig. 3.—*A*, nuclei in the normal sciatic nerve of the cat. The ruled line in *A* is equivalent to 0.04 mm. Cresyl violet stain.

B, segment twenty-one days after compression for two hours, producing paralysis for thirteen days. Cresyl violet stain.

C, edematous region proximal to an area of continuous compression by a 5 Gm. clip for thirteen days.

A stronger clip, of 430 Gm. tension, caused failure of conduction in ten to sixteeen minutes, and was left applied for a total of two hours. There resulted complete paralysis lasting eighteen, eighteen and eleven days respectively, in 3 experiments, with rapid recovery in contraction

recovery from the paralysis, there was no block of conduction on direct faradic stimulation of the nerve. No defect in sensation to pinch was found eighteen hours (an interval which allows recovery from anesthesia) after removal of the clip in any of these experiments. A brisk flexion

at the hip joint in response to very light touch to any part of the foot was noted in the later stage of the period of complete paralysis. Except for this "hyperesthetic reaction," it was not possible to be sure that sensation to touch was intact.

pressed area, showed the alternation in caliber of the myelin sheaths characteristic of the ischemic, or tourniquet, compression lesion previously described by us.[8] Widened nodes of Ranvier marked the transition from the normal nerve

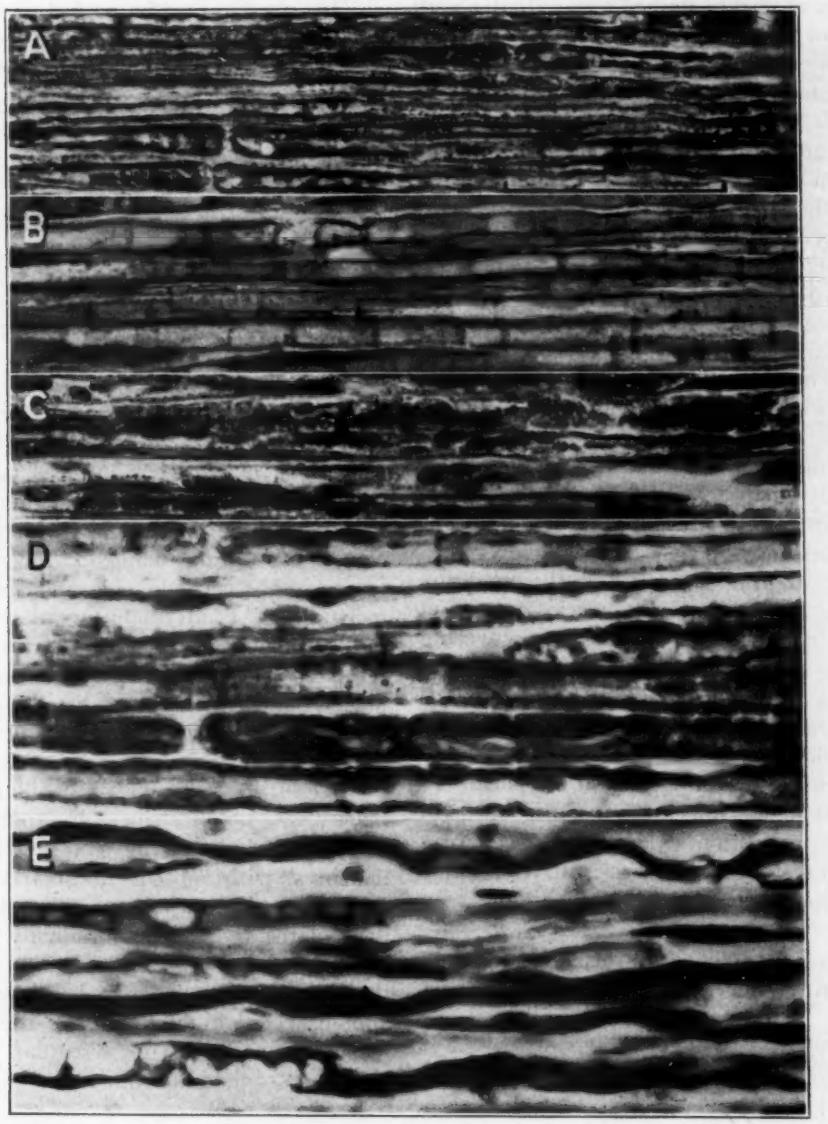

Fig. 4.—*A*, region of compression by a 7 Gm. clip for thirteen days, with no block. The ruled line in *A* is equivalent to 0.1 mm. Osmic acid stain.

B, edema of area of swelling below the region of application of a 7 Gm. clip for thirteen days. Osmic acid stain.

C, globular swelling of myelin in the most distal part of the proximal region of edema; from the same experiment as that from which sections shown in *A* and *B* were taken.

D, higher magnification of the globular swelling shown in *C*. Osmic acid stain.

E, axis-cylinders in the same region as that shown in *D*. Magnification same as that in *D*. Gros-Bielschowsky method.

The nerve in each case revealed sparse wallerian degeneration, more evident in the peroneal than in the popliteal division. The remaining fibers, in their passage through the previously com-

to the lesion. The axis-cylinder as it passed through each "gap" was usually covered by a very thin myelin sheath. Immediately below the level of previous compression the gaps in the

myelin were better covered, but for the next 15 mm. distal to this point the proximal end of each myelin segment was vacuolated, thin and irregular, with gradual transition to normal myelin beyond this zone. Stains for axis-cylinders showed the characteristic alteration of broad, short lengths of darkly stained axis-cylinder with either narrow, argentophilic threads or pale unstained axon. Lack of staining of the axis-cylinder was related to loss of myelin over the same "gap." This histologic picture was still present three, seven and eight weeks respectively after the clip had been applied (fig. 2 *C*). After even the longest of these intervals the previously compressed piece of nerve was swollen and darker than the rest; the vessels were congested, and a moderate degree of proliferation of endoneural cells and occasional lymphocytes remained (fig. 3 *B*). In places there was edema under the perineurium. The cellular reaction spread distally and proximally for 10 to 25 mm., being coextensive with edema, vascular congestion and changes in nerve fibers. The swelling of the nerve was due partly to swelling of the individual fibers and partly to separation of individual nerve fibers by exudate.

Particular attention was paid to the condition of the gaps in myelin eight weeks after full recovery of conduction. The myelin covering the gap (fig. 2 *E*) was as thin as it was ten to fourteen days after compression. The axis-cylinder in the gaps had, however, the appearance of a skein, like that of a condensation of neurofibrils in thick meshes (fig. 2 *D*) at the periphery of the axoplasm, an appearance consistent with that of slow restitution. The myelin covering the intermediate segments was still irregularly swollen and stained unevenly with osmic acid (fig. 2 *E*).

There was no evidence of formation of new vessels within the nerve bundle.

EFFECT OF LONG-CONTINUED PRESSURE

Clips of 2, 5 or 7 Gm. Tension.—Such clips when applied to the sciatic nerve could remain in position for fourteen days without any defect in conduction, whether tested by walking ability, placing reactions, spreading of the toes or reaction to pinch of the toe pads in the unanesthetized animal or by stimulation of the exposed nerve above and below the clip with the animal under light anesthesia. After fourteen days the compressed segment of nerve was, nevertheless, greatly thinned and flattened by the continued pressure, and the nerve fibers were more tightly packed than in normal nerve. The transition above and below the clip was one of abrupt swelling of the nerve, up to 150 per cent of its normal diameter, with gradual resumption of the normal diameter over the next 5 to 10 mm. beyond the plates. The spring and plates had excited an intense inflammatory reaction to the wax-coated metallic surface. This reaction did not penetrate the epineurium of the nerve.

The myelin sheaths and axis-cylinders were greatly changed in the compressed segment and at the region of emergence from under the clip, both proximally and distally. The myelin sheaths became regularly widened as they were followed distally in the first transition from normal nerve, appearing identical with those shown in figure 4 *B*, and at the height of the swelling they became irregularly thickened (fig. 4 *C*), though still wider than normal and less closely packed. At the beginning of the compressed area the nerve suddenly narrowed to 50 or 60 per cent of its normal diameter and throughout the region of compression the myelin sheaths were narrow, closely packed and granular, though regular in staining reaction (fig. 4 *A*). Myelin bordered each node of Ranvier but was paler than elsewhere. Immediately on emergence below the clip, where the nerve again widened to 150 per cent of its normal diameter, the myelin sheaths were loosely packed, wide and regular, and the incisures of Lantermann were prominent (fig. 4 *B*). The nodes of Ranvier were bordered by reticulated myelin. The axis-cylinders were not uncovered. About 3 mm. distal to the clip, where the nerve was still greatly swollen, the sheaths exhibited the same internal irregularity as at the height of the proximal swelling. This irregularity was identical in each situation and began as periodic bulging into the myelin tube at the incisures, with subsequent great thickening and contortion of the whole tube (fig. 4 *D*). Farther distally the irregularity gradually lessened until normal myelin was reached, 5 to 10 mm. from the clip. Both above and below the clip the simple, regular dilatation of the myelin tube was proximal, and the irregular swelling with distortion of the inner lumen distal, to the regular tubes.

Stains for axis-cylinders (Bielschowsky, Bodian) revealed striking changes. Throughout the area of swelling proximal to the site of compression, all axons were greatly increased in diameter, the size being maximal at the region of greatest swelling, 1 mm. from the clip. At the region of greatest increase there then appeared irregular erosions (fig. 5 *A* and *B*), each corresponding to a globule of myelin as seen in osmic stain (fig. 4 *D*). This zone passed into one of irregular excrescences and appendages (fig. 5 *A*) just before the axons converged into the compressed area. Here they lay tightly

packed (fig. 5 *C*) but had an irregular outline, with a vacuolated appearance. There were many appendages throughout. As the fibers diverged below the clip, their diameters increased again to approximately twice the normal, at first with regular outline, although a little more distally irregular erosions again appeared (fig. 5 *D*). In the region of greatest swelling of the nerve there were many small excrescences. The irregularity in outline and diameter of the axons gradually lessened as the distal swelling was passed and was absent in the remainder of the peripheral nerve. All fibers underwent the same changes. These changes were coextensive with the edematous swelling of the nerve on either side of the site of compression.

Also coextensive with the edematous swellings was a moderate increase in cellularity of the nerve. This increase was almost wholly due to the presence of large numbers of flat cells with large, pale nuclei, many circular and many oval, and long finger-like processes of cytoplasm, containing small vacuoles (fig. 3 *C*). These were undoubtedly endoneural cells. There were occa-

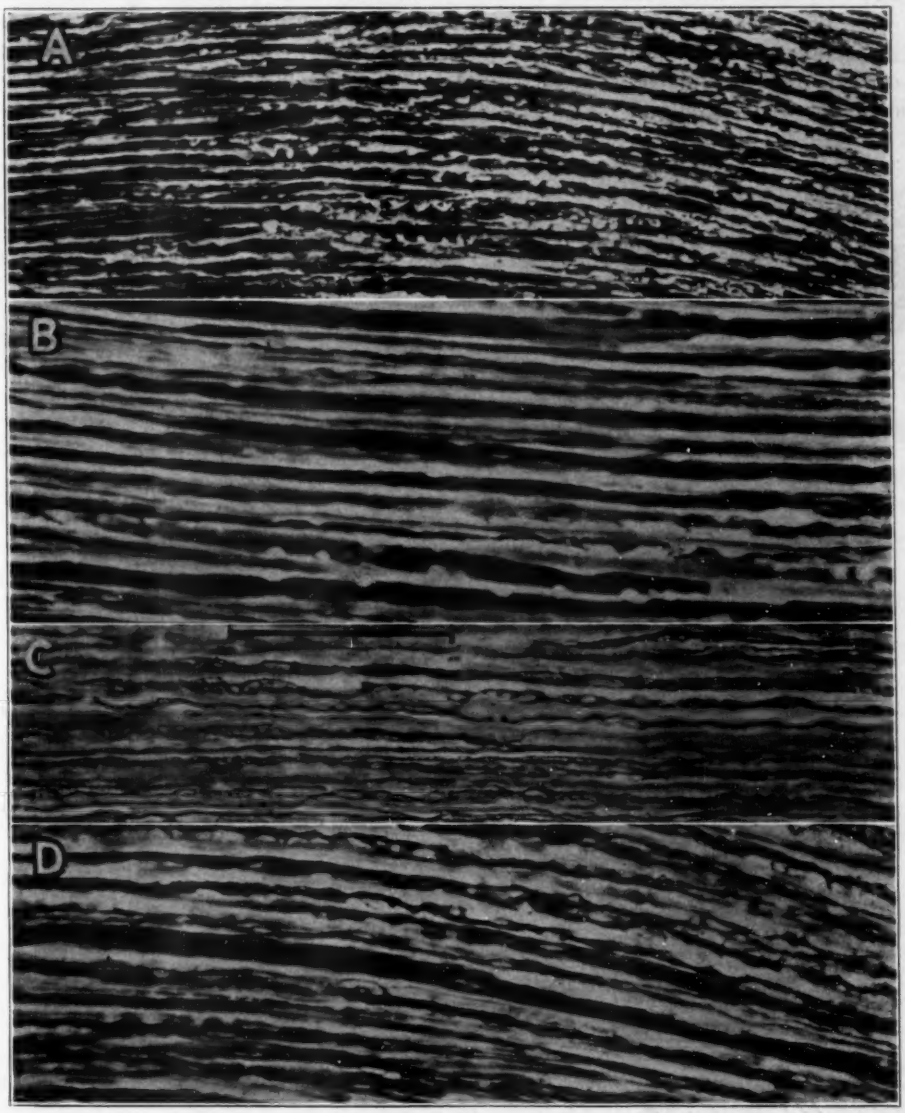

Fig. 5.—*A*, height of swelling of nerve proximal to area of compression by a 7 Gm. clip for thirteen days. The proximal portion is to the left of the figure. Gros-Bielschowsky method.

B, higher magnification of the swollen axis-cylinder shown to the left of *A*. The ruled line for *B*, *C* and *D* is equivalent to 0.1 mm.

C, axis-cylinders from the area under the clip; from the same nerve as that shown in *A*.

D, height of swelling of axis-cylinders distal to the area of application of the clip, from the same nerve as that shown in *A*.

sional lymphocytes, many possessing a notched border, with no visible cytoplasm in the Nissl or hematoxylin preparations. The Schwann cells appeared not to have changed. Occasional mast cells and rare plasma cells were encountered. In the compressed segment the Schwann cells were unaltered, and the endoneural cells were only slightly increased, with occasional lymphocytes.

Close inspection of the myelin sheath in the regions of greatest irregularity revealed that small nodules of myelin bulged into the inner cavity, these enlargements producing the indentations in the axis-cylinder (figs. 5 *D* and 4 *E*). The absence of free fat and of cellular reaction within the sheath of Schwann indicated that the change was of passive character. The appearance was consistent with irregular, simple swelling of myelin. The close association between the degree of this swelling and the degree of separation of the nerve fibers by fluid appears to indicate that the condition was, in fact, edema of myelin. The gross distortion of the fluid axon in relation to the irregular swelling of myelin was present in every fiber in the sections, so that there is no doubt that these fibers, both motor and sensory, were conducting. We regard these structural alterations as passive distortions consequent on the vascular narrowing, with congestion above and below. They are of interest in so far as they were not associated with any disorder of function.

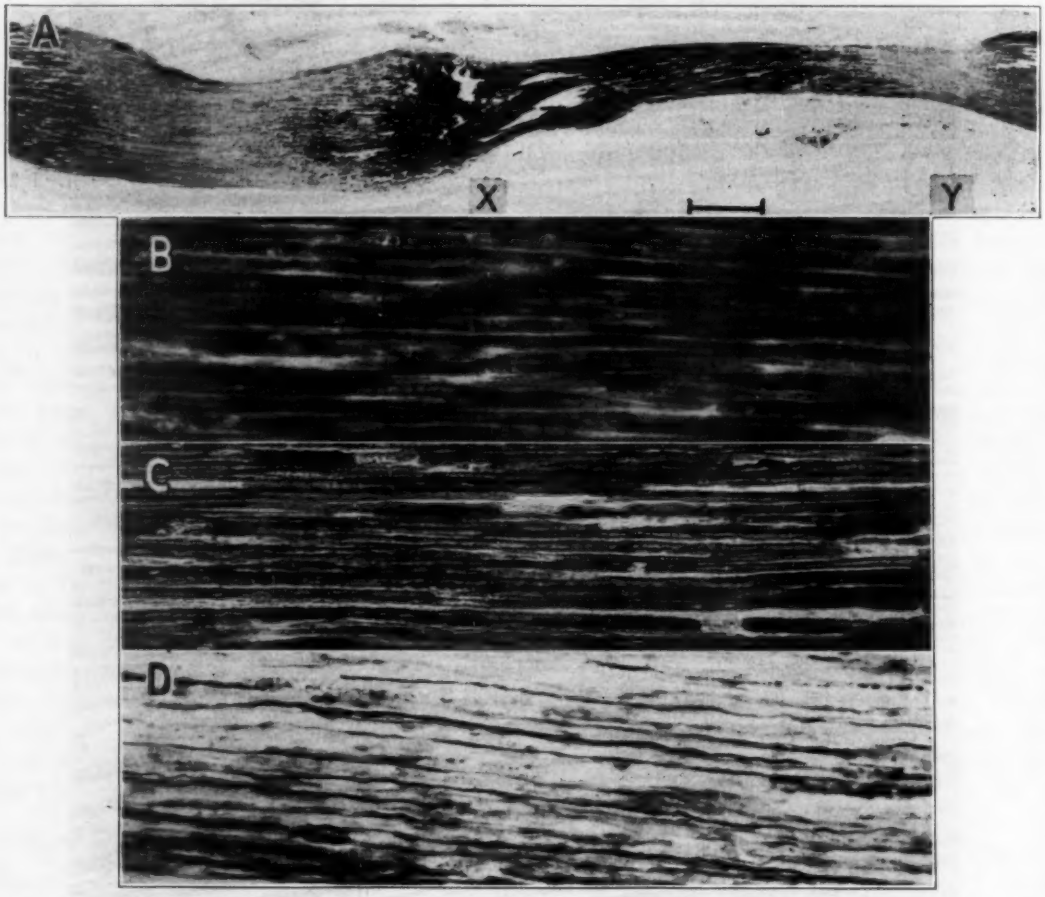

Fig. 6.—*A*, low magnification of the popliteal nerve which had been compressed in area *X* to *Y* by a 44 Gm. clip for twenty days. The proximal portion of the nerve is to the left of the figure. The ruled line is equivalent to 1 mm. Osmic acid stain.

B, compressed segment shown in *A*, under higher magnification.

C, "gaps" in the myelin 7 mm. proximal to *X* (*A*), under higher magnification.

D, axis-cylinders in the necrotic segment. Gros-Bielschowsky method.

Clip of 44 Gm. Tension.—Such a clip, when left in place, resulted in persistent and complete motor and sensory paralysis. Exploration of the nerve after fifteen days in 1 animal and after twenty-one days in another revealed complete loss of all electrical excitability of both sensory and motor fibers below the clip, with complete histologic degeneration of all fibers in the nerve

and of all motor nerve endings and with atrophy of muscle fibers. The compressed segment of nerve was extremely flattened, with the usual abrupt transition to swelling of the nerve on its emergence from the clip. In the compressed segment there was preservation of both axis-cylinders and myelin (fig. 6 *A*). The myelin was in the form of narrow, thick-walled tubes of a homogeneous, finely granular structure (fig. 6 *B*). In places a coarse granule occupied a small, pale cavity. No recognizable nodes remained. At the edges some dissolution and fine fragmentation had taken place. There were some coarse granules in fat cells, both proximally and distally, but they were more numerous in the former situation. The axons were tortuous and irregular, and the ground substance had some affinity for silver (fig. 6 *D*). No cell nuclei were

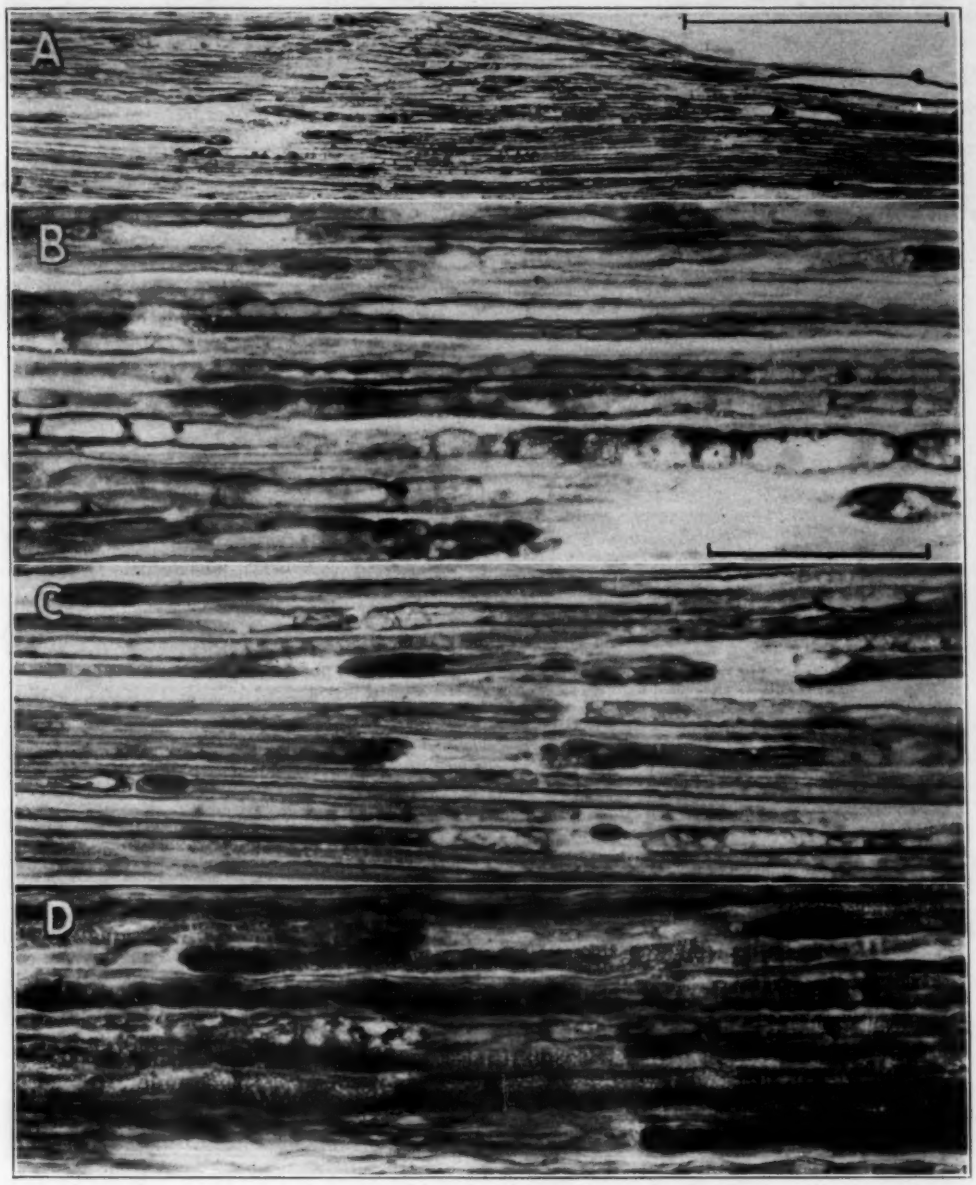

Fig. 7.—*A*, height of swelling just proximal to an area of compression by a 10 Gm. clip applied for fifteen days. The most proximal region of compression appears to the right of the figure. The ruled line is equivalent to 0.5 mm. Osmic acid stain.

B, higher magnification of a portion from the center of the field shown in *A*. The ruled line for *B*, *C* and *D* is equivalent to 0.1 mm.

C, section similar to that shown in *B*, illustrating gaps in myelin.

D, portion of nerve under the clip.

stainable in this region except at the margins. It was clear that both myelin and axis-cylinders were necrotic and that the absence of phagocytosis and the further breakdown of both structures was related to the absence of blood supply and of natural phagocytes. Phagocytosis was present within 0.5 mm. of each end of the compressed region, and from this point into the swollen sections of nerve adjacent to the clip all trace of recognizable sheaths and axis-cylinders had disappeared. The distal segment of nerve showed all the phenomena of wallerian degeneration. These changes were more advanced in the edematous region immediately adjoining the clip, where all ellipsoid bodies had disappeared. Proximal to the clip the nerve had also degen-

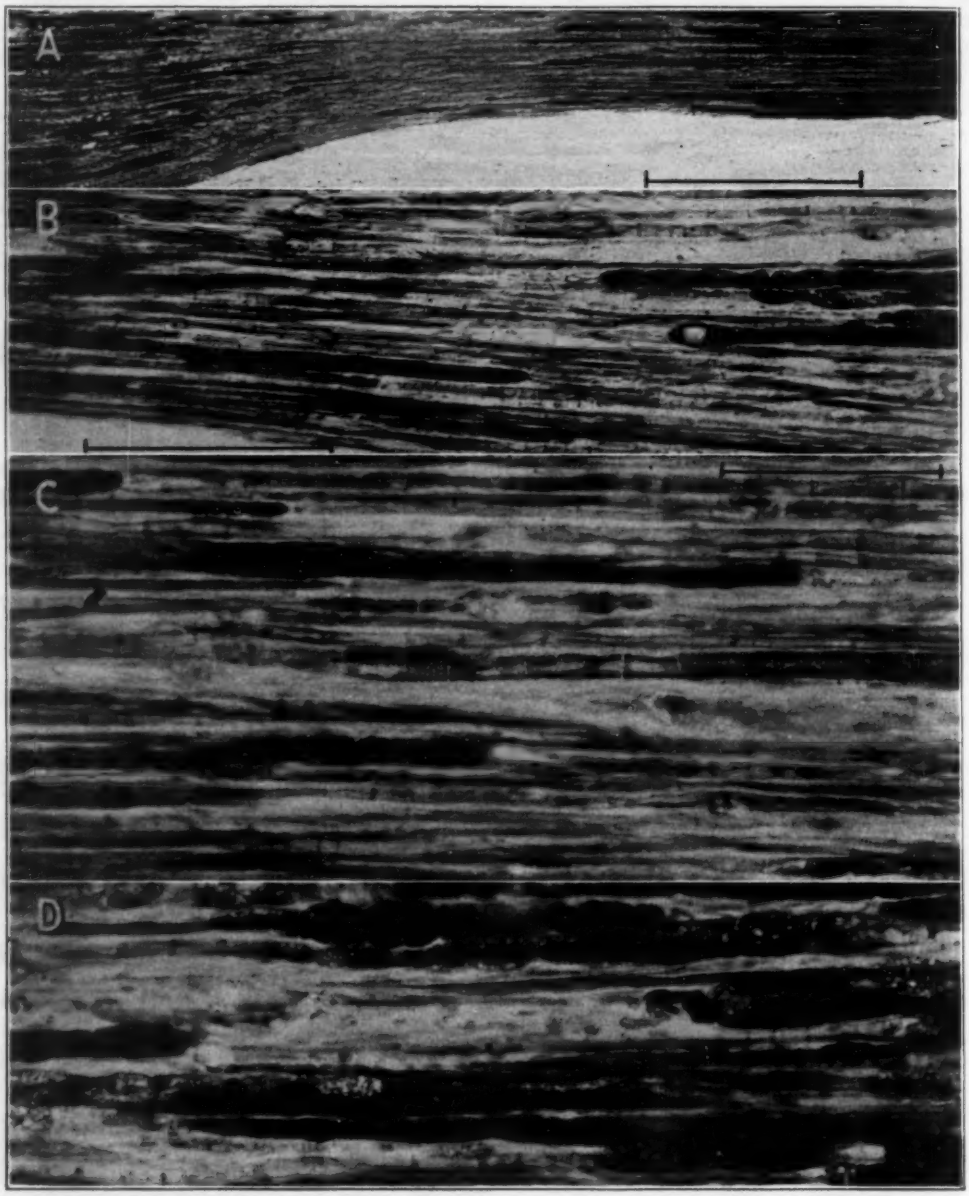

Fig. 8.—*A*, section from the same experiment as that in which the segment of nerve shown in figure 7 was taken. The nerve is emerging from the distal end of the clip. The compressed area is to the right. Osmic acid stain. The ruled line in *A* and *B* is equivalent to 0.5 mm.

B, nerve fibers emerging from the distal extremity of the area to which a 10 Gm. clip was applied for forty-one days. The distal portion is to the right of this figure, and of the remaining figures. Osmic acid stain.

C, higher magnification of *B*, showing transition of the myelinated to the demyelinated region. The ruled line for *C* and *D* is equivalent to 0.1 mm.

D, section from a region distal to that shown in *C*, illustrating transition to full myelin.

erated for 6 mm. The proximal limit of myelin was irregular, and many wide nodes were seen just above the last globule of myelin (fig. 6 *C*). The axis-cylinders ended in loops, spirals and knobs, all corresponding to the limit of the myelin. From the stumps of axons fine sheaves of regenerating filaments extended into the proximal zone of demyelination, there to become lost in faintly staining, abortive loops and bundles. None of these had reached the region of nerve lying under the blades of the clip.

fifth, sixth or eleventh day (6 observations). Three or four days later slow recovery commenced, with almost complete restoration of function, including spreading of the toes, by the twenty-sixth day. When clips of this intermediate degree of tension were used, no defect in gross sensation, as judged by the response to pinch of a toe pad or a heel pad, was observed except that in the paralytic period mere contact with the foot often elicited withdrawal of the affected limb (hyperesthesia [?]). Electrical stimulation

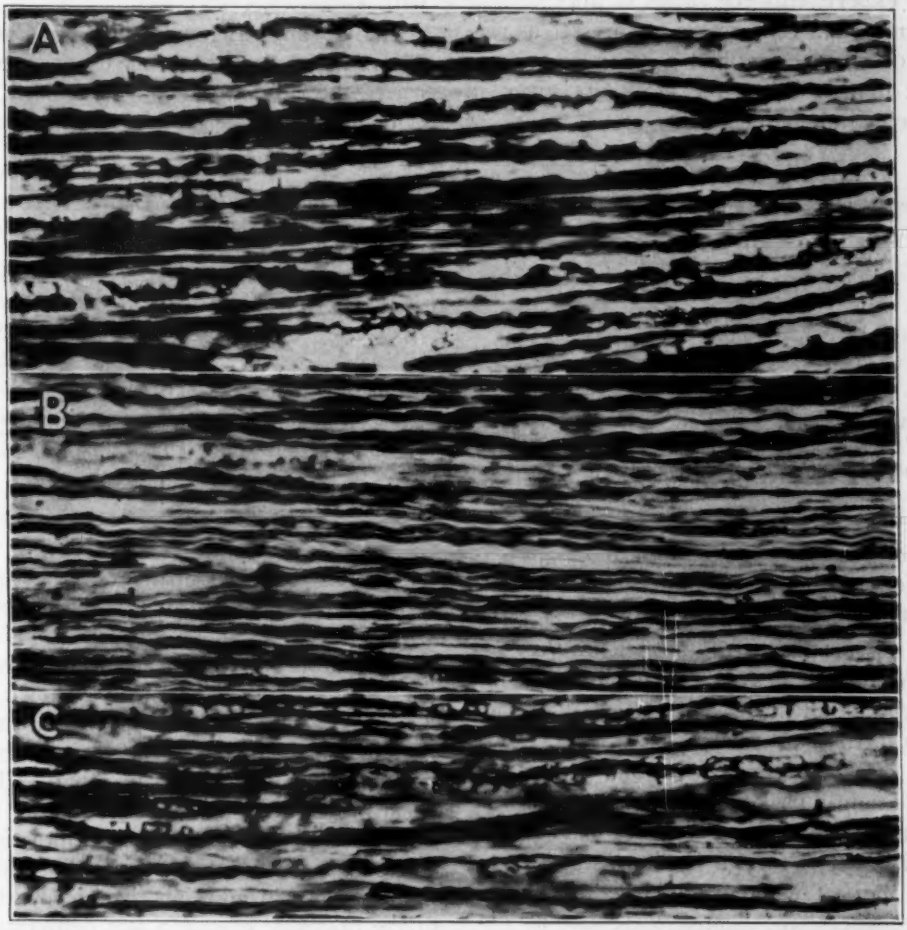

Fig. 9.—Changes in axis-cylinders induced by application of a 10 Gm. clip for forty-one days, with complete nerve block from the fifth to the eleventh day. No block was present when the animal was killed. Gros-Bielschowsky method; magnification same as that in figure 8 *C* and *D*. *A*, height of swelling proximal to the clip; *B*, section from area under the clip, and *C*, height of swelling distal to the clip.

Clips of 9 and 10 Gm. Tension.—Compression with such clips induced no immediate paralysis, but after twenty-four hours (and not until the sixth day in 1 animal) delayed onset of paralysis occurred. Spreading of the toes was first noted to be defective: the following day dorsiflexion and plantar flexion of the foot were slightly weak, this impairment progressing to severe paralysis of all movements of the toes and ankles on the

of the exposed nerve, with the animal under light anesthesia induced with pentobarbital sodium, during the paralytic stage showed that the nerve block had all the characteristics of the paralysis described earlier (Denny-Brown and Brenner [8]) as ischemic paralysis induced by application of a tourniquet. The nerve below the region of compression remained excitable, so that electrical stimulus produced a strong muscular contraction

(75 to 100 per cent of normal) and a reflex response in the animal of a degree comparable to that from a control sensory nerve or from the same nerve above the lesion. The retention of electrical excitability in spite of paralysis lasted as long as eighteen days, well beyond the transient persistence of excitability in a segment of nerve below a complete section. The amount of conduction of motor impulses through the region of block at the final examination was variable, depending on the stage and the degree of paralysis. In 6 experiments the ratios of approximate power of muscular contraction (expressed as percentages of normal pretibial contraction) above the block to that below the block are given in the following tabulation:

Compression Gm. Tension	Duration of Paralysis, Days	Duration of Experiment, Days	Degree of Recovery at End of Experiment	Conductivity When Nerve was Explored (Peroneal Only)*
10	Complete 7-14	17	Still weak	5 : 75
9	Weak 7-10	17	Full recovery	100 : 100
10	Complete 6-13	15	Very weak	50 : 100
9	Complete 6-14	18	Very weak	25 : 100
10	Incomplete 4-11	41	Full recovery	100 : 100
10	Complete 5-11	41	Full recovery	100 : 100

* The ratios in the last column are those of the percentage strength of contraction of pretibial muscle for maximal stimulation above the lesion to the percentage strength of contraction below the lesion. In the case of the last ratio, the popliteal nerve had slipped from between the plates of the clip and was compressed between two of the brass wires. The popliteal nerve remained under the plates, and the figures given are for the muscles of the calf.

In these experiments, as with all other experiments with maintained pressure, the region of compression of the nerve was greatly thinned, and neighboring segments were swollen.

Lesion Associated with Transient Pressure Block.—A notable degree of histologic change was present at all stages in the evolution and involution of the paralysis.

Region of Compression: In this area nerve fibers were tightly packed and the myelin sheaths thin but intact (fig. 7 *D*) except for intermittent loss in thickness of myelin in short segments of 0.1 to 0.2 mm. Owing to the close approximation of the fibers, the "gaps" were not as distinct as in tourniquet experiments. They were few in the proximal part of the compressed segment (fig. 7 *D*) but rapidly became more frequent, and each was longer as the distal part of the compressed area was approached. Many of the gaps were completely devoid of myelin when the compression had lasted fourteen days or less. After compression for twenty-one days it was exceptional to find a gap without a thin coating of myelin. The demyelinated gaps were identical with those we have previously described [8] in nerves subject to tourniquet paralysis. In most instances the myelin was all reduced to pale, thin tubes for the last millimeter of compression and beyond (fig. 8 *A* and *C*).

The axis-cylinders were tightly packed together, with intermittent pale or unstained gaps (fig. 9 *B*). There was occasional vacuolation. Toward the distal end of the compressed segment there was intermittent beading of axis-cylinders in silver stains (fig. 9 *B*), often with very fine or unstained connecting axon links. In the segment in which all large myelin sheaths had disappeared the axis-cylinders were all thin and were impregnated faintly and unevenly with silver (fig. 10 *C*).

Above and Below Area of Compression: Above and below the compressed piece of nerve, where the caliber suddenly increased, there was evident edema. Here the myelin was greatly altered. The degree of change coincided with the degree of edematous expansion of the nerve. The most proximal change in the myelin was a widening in diameter of the whole sheath, with lessened thickness of myelin. This occurred as the nerve entered the proximal swelling and was identical with the change shown in figure 4 *B*. As the zone of maximal edema was reached, the myelin bulged irregularly into the tube in places and ballooned out in others. The whole sheath was seen to be narrowed as the nerve was followed into the area of compression. These changes were identical with those caused by lighter clips; in addition, just before the height of the proximal edema, a few demyelinated gaps were noted (fig. 7 *C*). Such gaps were relatively infrequent up to the middle third of the compressed zone. Distally, beyond the clip, the myelin had disappeared for a space of 0.5 to 1 mm. (fig. 8 *A*), beginning again suddenly in large knobs (fig. 8 *D*), beyond which irregularly swollen myelin with widened nodes made a gradual transition to normal sheaths 5 to 15 mm. from the clip.

The axis-cylinders entering the proximal swelling became at first swollen and then irregular, as with the simple edema of lesser compression. The excrescences in the irregular

state were often extremely elaborate (fig. 9 *A*), corresponding to even larger swellings of the myelin sheath (fig. 7 *B*) than those produced by very light clips. With the occurrence of paralytic block, however, an additional change was apparent, namely, an intermittent paling of the axis-cylinder, corresponding to gaps bared of myelin. This type of change in the axis-cylinder was apparent throughout the lesion, both above and below the clip, and, corresponding to the myelin gaps, became general at the distal extremity of the compressed zone (fig. 10 *A* and *B*). Distally the axis-cylinder was unevenly stained, greatly attenuated and sinuous until the region of greatest distal edema was reached (fig. 10 *C*). Here, there was a sudden, but irregular, increase in caliber (fig. 10 *D*). Unstained or partly stained gaps were still frequent beyond this point, with many excrescences from the larger axons (fig. 9 *C*). There were then gradual

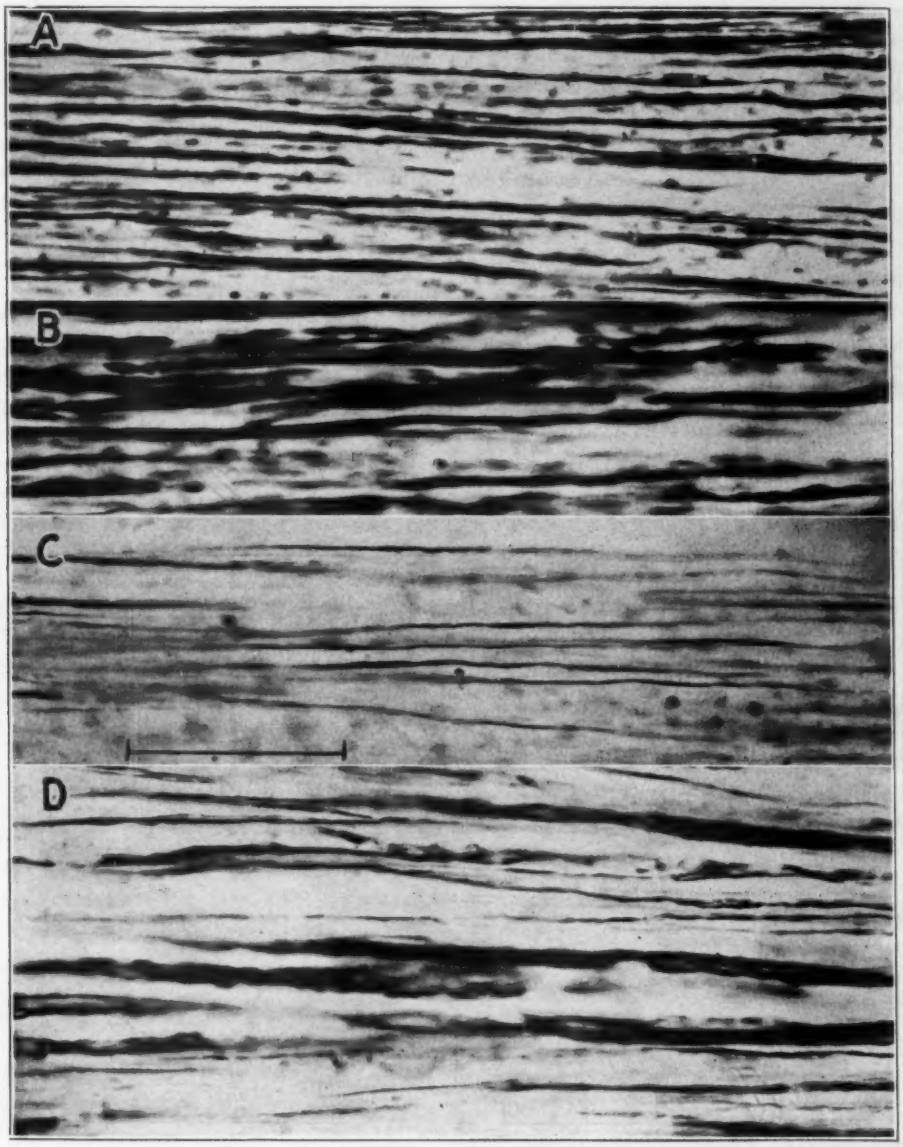

Fig. 10.—*A*, axis-cylinders at the distal end of the compressed region to which a 9 Gm. clip was applied for seventeen days. Gros-Bielschowsky method, counterstained with cresyl violet.

B, axis-cylinders at distal end of the compressed region to which a 10 Gm. clip was applied for forty-one days.

C, section from a region similar to that shown in *A*, showing demyelinated axons emerging from under the distal end of the clip. The ruled line is equivalent to 0.1 mm.

D, section taken farther distally than that shown in *C*, illustrating region of junction with normal fibers.

lessening of diameter and resumption of regularity as the axons were traced beyond the zone of edema into the distal nerve. The changes in the axis-cylinders, therefore, corresponded accurately with the alterations in myelin. The muscular nerves and nerve endings were unaffected. In some nerve bundles isolated fibers in wallerian degeneration were present; they were more frequent in the peroneal than in the popliteal nerve. Our best examples of a pure pressure lesion were in the popliteal nerve, which has already been noted as being more resistant to pressure lesion produced by tourniquet (Denny-Brown and Brenner [3]).

As we have already described, in the pressure lesion produced by tourniquet the altered axoplasm, besides losing affinity for silver, gains in affinity for iron hematoxylin, and at a delicate stage in differentiation with this stain the demyelinated portion of the axon is darkly stained and the rest of the axon is unstained. In such preparations it is evident that the altered axis-cylinder corresponds exactly to the demyelinated gap, for the normal myelin is also stained. The same staining of the altered region is seen in sections prepared with Mallory's phosphotungstic acid hematoxylin. Neither method gives as clear and as certain a result as does silver impregna-

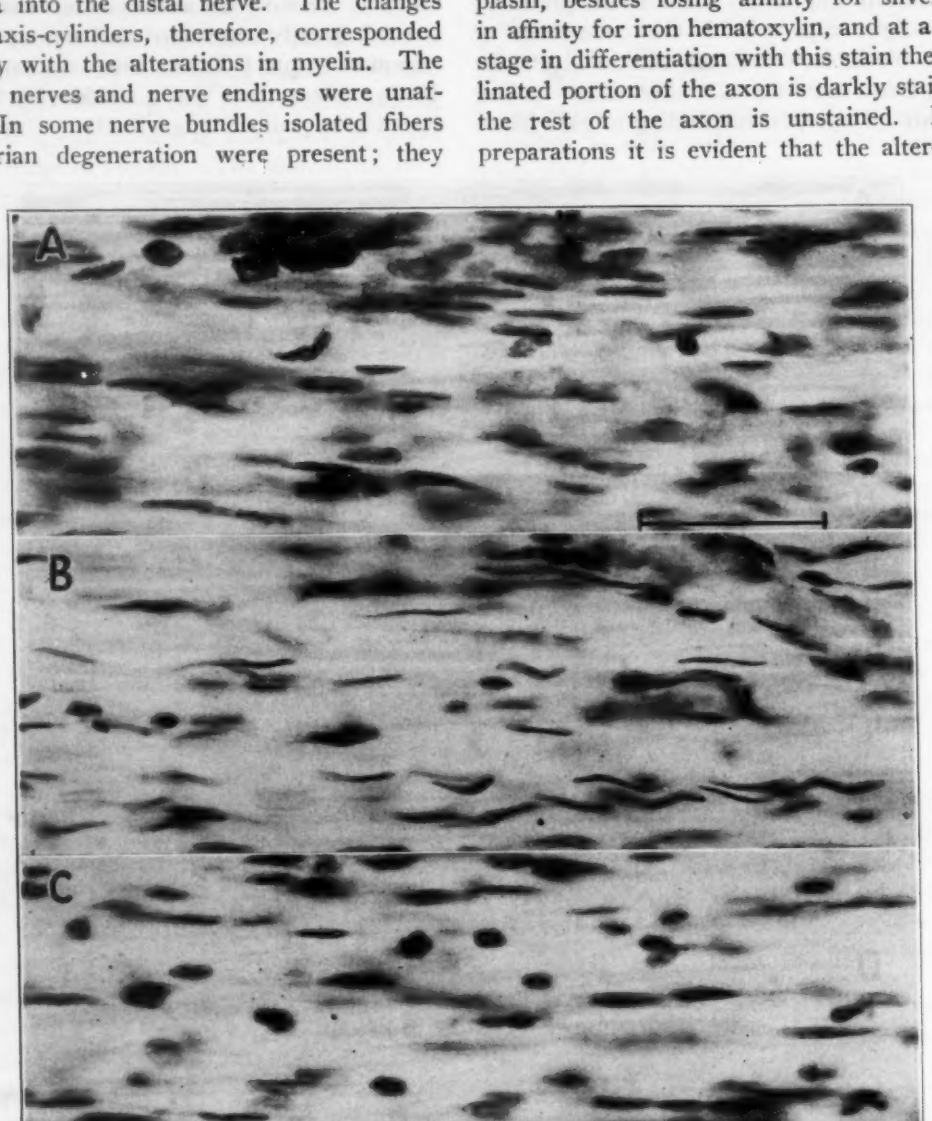

Fig. 11.—Cell changes. The ruled line is equavalent to 0.04 mm. for *A*, *B* and *C*. Cresyl violet stain. *A*, section from the area of greatest edema, just above the area of compression by a 10 Gm. clip for forty-one days; *B*, section from the compressed region, in the same experiment, and *C*, section from the demyelinated region, in the same experiment.

tion. The change is not a condensation of neurofibrils.

As in tourniquet lesions, all types of fibers were affected in the pure pressure lesions. It was clear in the Bielschowsky sections that the fine axis-cylinders in the demyelinated gap still varied considerably in size, so that nonmedullated fibers were seen only as intermittent thin streaks. It was difficult to follow the changes at the junction with myelin, but the axis-cylinder appeared first to swell, though it stained poorly with silver (upper border of fig. 10 *D*), and then made a sudden transition to a broad, densely stained band. About 0.5 to 1 mm. farther distally, the broad band became extremely irregular, with excrescences, before making a gradual transition to a normal appearance 2 to 10 mm. farther on. After the lesion had persisted from six to eight weeks, the axis-cylinders nearly all stained deeply with silver, and pale gaps were difficult to see, though there was great thinning in all fibers in the demyelinated area.

Cell stains (cresyl violet) revealed a great increase in cellularity in the proximal edematous region (fig. 11 *A*). The increase was chiefly due to the presence of great numbers of large, pale endoneural cells, with macrophages and occasional lymphocytes, as with simple edema. The Schwann nuclei were a little more swollen than normal but were not increased in number. When a gap in the myelin occurred, the endoneural cell was wrapped obliquely around the axon, and a nearby "polyblast" macrophage contained a few granules of fat. In the compressed zone (fig. 11 *B*) the Schwann nuclei stained less well but showed no other change. There was a slight increase in the number of endoneural cells and lymphocytes. The endothelium of vessels appeared to be unaffected. In the edematous area distal to application of the clip (fig. 11 *C*) the macrophages and gitter cells frequently contained fat in small granules, though nowhere in large granules or in great quantity unless wallerian degeneration had complicated the lesion. The phagocytes did not enter the sheath of Schwann, nor did the myelin break up into segments, ovoids or "digestive chambers," as in wallerian degeneration. The demyelinated axons were accompanied by chains of Schwann cells, little, if at all, more numerous than normal, and each sheath of Schwann was encircled at intervals by endoneural cells (fig. 11 *C*). There was no invasion of the Schwann sheath by phagocytes.

COMMENT

The experiments described in the preceding section served first to identify the events of tourniquet paralysis and those following direct pressure on a nerve and then made possible an analysis of the complex changes following continued compression.

Transient Pressure.—The first series of experiments, concerned with the effect of transient (two hour) severe pressure on a segment of nerve, show that the resulting nerve lesion is in every way comparable to the effect of application of a narrow tourniquet to the whole limb for a similar period, as previously described (Denny-Brown and Brenner [3]). The histologic lesion is identical, namely, the appearance of gaps in the myelin covering of the nerve fiber, with change in the staining qualities of the axoplasm in the demyelinated section. In addition, the whole previously compressed section of nerve becomes edematous and is permeated by wandering endoneural and mesodermal cells. The histologic changes appear only after two to four days and are associated with a conduction defect. A metal clip more readily provokes some degree of wallerian degeneration than does application of a tourniquet, but even when such degeneration is widespread, any surviving fibers show the characteristic alternation of staining of the intermediate degree of presssure lesion. It is likely that any form of pressure directly applied to a nerve will, by angulation and unequal stress, cause physical injury besides the ischemia produced in pure form by tourniquet compression, so that wallerian degeneration of some fibers may be expected.

The defect or block in conduction produced by application to the nerve of such a clip is selective. Sensation is little, if at all, damaged by a degree of lesion which causes complete motor paralysis lasting nearly three weeks. Recovery of conduction, once begun, is extremely rapid. It is surprising, therefore, that after as long as eight weeks the lesion presents an appearance closely resembling that after two weeks. Restitution of myelin is evidently a slow process. The axis-cylinder, on the other hand, shows some renewed affinity for silver after such a period. The meaning of continuing edema and the presence of scavenger cells is obscure.

The earliest sign of reaction of a nerve to pressure is swelling of the axis-cylinders, usually associated with appearance of clear spaces or notches in the outline of the axon, which we called "vacuolation" in our previous paper.[3] From the material here presented it appears that many of these "vacuoles" may be only indentations of the axis-cylinder produced by budding of the myelin into the cavity of the myelin tube, which indents the axon. Such axonal swelling was also encountered as a persistent and obvious change when the initial ischemia was too brief

or incomplete to produce conduction block. It was then associated with edematous swelling of the previously compressed segment and was coextensive with such swelling. This change was also notable in tourniquet lesions. It is strictly limited to the segment which was previously ischemic and is always accompanied by edema and swelling of the nerve. When moderately severe, it is associated with the appearance of occasional lymphocytes between the nerve fibers. The Schwann cells are unaltered. The cytoplasm of the cells of the endoneurium becomes more obvious and vacuolated, but there is no nuclear change. The perineural space is not enlarged.

Such edema was also encountered in some fasciculi of the sciatic nerve when all the vasa nervorum to the nerve in the gluteal region, thigh and popliteal space were ligatured, and was identical with that shown in figure 2 *A*. As we showed in our earlier paper, this procedure did not impair the conduction of the nerve. Such swelling of axis-cylinders and vacuolation may therefore be considered a benign change. There is no associated damage to myelin. The extensive longitudinal anastomosis of vessels in peripheral nerve is well known (Adams [8]), and, in a series of rabbits, Adams [9] observed no degeneration in 10 animals and degeneration in 2 others after the same procedure.

Although loss of myelin is such a prominent feature of the ischemic lesion, it is also noteworthy that the Schwann cells show little, if any, reaction to this change, in marked contrast to their behavior when wallerian degeneration occurs. Conversely, the restitution of myelin, which appears as a very thin covering in the second week after injury, makes little progress in the following weeks, long after recovery of conductive function. Further histologic recovery appears to await restoration of the full argentophilic property of the bared segment of axis-cylinder. None of these changes interferes with the trophic influence which the nerve cell exerts on its peripheral segment or on the muscle fiber it controls.

Continued Pressure.—The second series of experiments introduces additional factors. Continued pressure on a segment of nerve not only renders that region ischemic but induces prolonged vascular stasis in neighboring regions. The process of repair in the compressed segment is hindered or abolished. It is not surprising, therefore, that when such compression is severe, the affected segment is preserved in a state of ischemic necrosis, with myelin and axis-cylinders intact. The neighboring segments, both proximal and distal, degenerate. The nearest surviving myelin on the proximal segment shows gaps at the nodes, a change revealing that the disorder here is also ischemic. Herein lies the explanation of an old controversy between Ramón y Cajal,[10] von Bungner [11] and others. Cajal maintained that the proximal degeneration of myelin following a transverse lesion of nerve extended only to the next proximal node, or a shorter distance. Von Bungner and others asserted that it extended proximally for two nodal segments. With ligature of the nerve (von Bungner's method) the proximal ischemia is much more extensive than with simple section of a small nerve bundle, as performed by Cajal, in which case collateral circulation is rapidly established through surrounding tissue.

Continuously applied pressure deforms the nerve. Pressures of 2 to 7 Gm. greatly narrow the compressed segment and induce edema above and below. Function, however, is not impaired. Again, as with transient pressure, it is remarkable to what degree disorder of structure can progress without impairment of function (fig. 5). The primary change appears to be a budding of the myelin into the interior of the sheath. The buds occur first at natural folds, such as the Schmidt-Lantermann incisures, but later become general. The grotesque distortions of the axis-cylinder appear to be the result of displacement of the fluid axon into the crevices between the myelin swellings. There is no degeneration of myelin and no cellular reaction except an increase in the large endoneural cells, many of which show pseudopodia. Comparison of these large vesicular nuclei with the swollen astrocytes seen in cerebral edema reveals a parallel in reaction and contour that convinces one of an essential identity of performance. This phenomenon of edema of nerve without disorder in function is one we have not found described in the literature.

The swelling of nerve on either side of an arterial cuff described by Weiss and Davis [12] and by Weiss [13] is undoubtedly the process which

8. Adams, W. E.: The Blood Supply of Nerves: I. Historical Review, J. Anat. **76**:323-341, 1942.

9. Adams, W. E.: The Blood Supply of Nerves: II. The Effects of Exclusion of Its Regional Sources of Supply on the Sciatic Nerve of the Rabbit, J. Anat. **77**:243-250, 1943.

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11. von Bungner, O.: Ueber die Degenerations- und Regenerationsvorgänge an Nerven nach Verletzungen, Beitr. z. path. Anat. u. z. allg. Path. **10**:321-393, 1891.

12. Weiss, P., and Davis, H.: Pressure Block in Nerves Provided with Arterial Sleeves, J. Neurophysiol. **6**:269-286, 1943.

13. Weiss, P.: Endoneural Edema in Constricted Nerve, Anat. Rec. **86**:491-522, 1943.

we have observed. These authors noted that the proximal swelling was larger than the distal and hypothesized a centrifugal flow of neural and axonic fluid to account for the phenomenon. In their experiments the nerve had been sectioned distally for the purpose of applying the arterial cuff. This procedure interferes with the circulation of the peripheral segment, and the impaired blood supply, with the degeneration produced by their arterial cuff, accounts for the asymmetric swelling observed. We, therefore, cannot subscribe to the hypothesis advanced by Weiss [18] that the edema represents stasis of centrifugal flow of endoneural fluid. These authors also observed intact nerve fibers distal to an arterial cuff which caused transient block of electrical impulses and some degeneration in other fibers. Further experiment is required to show whether or not intermittent occlusion with an arterial cuff will produce an ischemic lesion of the type we have described or, what is more likely, a more destructive lesion without dissociated effect on conduction.

At a pressure of 9 to 10 Gm. a critical value is reached. Impairment of function begins in one to six days and progresses to complete paralysis without sensory change in the next day or two. After ten to twenty-six days recovery commences and ultimately becomes complete, in spite of maintenance of pressure. The changes consequent on edema now have added to them the true ischemic lesion of discrete gaps of absence of myelin, identical with those produced by transient compression. The loss is greatest at the distal extremity of the compressed area, as the nerve fibers emerge from the clip. Here all myelin may be absent for a zone of 1 mm., which is the approximate length of one segment of myelin. In this situation, also, is observed the beginning of any degeneration if the pressure has been of critical value. This patchy dissolution of the myelin segment is the histologic sign of a pressure conduction block. The manner of disintegration is that of solution, thus differing from the direct phagocytosis of wallerian degeneration.

This "intermediate degree of pressure lesion," with block of motor impulses, but without degeneration of the peripheral nerve or muscle fiber, is associated with a considerable mesodermal cellular reaction. Both lymphocytes and macrophages invade the nerve. The chief differences between this reaction and that accompanying wallerian degeneration are the great amount of free fat and the formation of myelin ellipsoids, which characterize the latter. In the former reaction, the Schwann cells appear to remain quiescent, and the axis-cylinders maintain a precarious continuity of altered structure. The blood vessels appear unchanged, though on either side of the compression lesion there is considerable congestion of all vessels, to which, in our opinion, the edema of the nerve is attributable. There is no evidence of distention of the perineural space. The cellular changes and edema, together with the alterations in the nerve fiber, persist for a remarkable period, in spite of full recovery of function. Our impression is that after six and eight weeks the proliferated endoneurium throughout the edematous area is organizing. There is great difficulty in distinguishing the young fibroblast from an inactive Schwann cell, but no significant fibrosis had occurred. After survival for six months the myelin of the previously demyelinated segments was still extremely thin. The gaps were still obvious, also, in silver preparations. The endoneural nuclei and collagen were increased throughout the area of previous compression. These observations indicate that the prognosis of the compression lesion of nerve is benign.

With continuous compression sufficient to cause a pressure block the onset of paralysis was delayed, and after a period of block spontaneous recovery occurred. Though in early experiments the clip was sometimes found to have moved in its relation to the nerve, we were satisfied that the transitory course of paralysis was independent of such movement. It appears likely that at the low pressures involved, the pressure of the edema and exudate may succeed in equaling that of the spring. In this respect the spring clip fails to imitate a band of constricting scar tissue, which many observers have found to maintain a pressure lesion in man for many weeks or months. In such a lesion all the histologic features observed by us after eight weeks may be expected.

The lesion induced by light continuous compression has interesting physiologic correlations, which it shares with the effect of transient severe compression, either direct or by tourniquet. Conduction is abolished without loss of anatomic continuity, and motor conduction is selectively affected. In the experiments here reported, as in the production of a tourniquet lesion, the histologic picture gives no clue to the means of dissociation of paralysis. All sizes of fibers are affected. We have considered the possibility that the "gap" in sensory fibers might be shorter, or that a very thin coating of myelin might be retained, and the lesion thus differ qualitatively from the disturbance of motor fibers. Against this view is the great similarity of the demyelinated gaps in all fibers. The nerve shown in figure 8 *A*, for example, with all the fibers demyelinated at one level, was still conducting touch and pain sensations. It appears, therefore, that

the selectivity lies in the functional properties of the block rather than in the size of the fibers affected. The loss of myelin and the change in staining reaction of axoplasm are mutually associated, so that it does not appear possible to relate the loss of conduction to one or to the other, except in so far as the patchy loss of affinity for silver by nonmedullated fibers indicates a primary axonic lesion. It is now clear that the stasis of neural tissue fluids, with resulting deformity of the axon, is in itself an unimportant factor in the function of conduction. There is no evidence of circulation of fluid in the nerve trunk, for the edema was the same on both the proximal and the distal side of the compression.

Ramón y Cajal,[10] von Bungner [11] and others of the older investigators frequently used ligatures to produce a nerve lesion. Both Cajal and von Bungner described the persistence of preserved axis-cylinders, with absence of myelin and Schwann cells under the ligature. We have also examined this phenomenon and have noted that it is identical with the ischemic necrosis and preservation under a continuous severe pressure. The early disappearance of myelin under a ligature and its preservation under more extensive compression are related to the earlier absorption of the necrotic zone in the case of the former. Cajal spoke of "dislocation of myelin" above and below the ligature, to produce dilated sheaths. In our compression experiments there was no such dislocation, and the dilated sheaths above and below the clip were filled with edematous axoplasm or edematous debris, according to the severity of compression. Cajal also described experiments with moderately tight ligatures in which some of the central fibers of the nerve escaped necrosis. He noted thinning of the axis-cylinders and myelin as the fibers passed under the ligature, with resumption of normal diameter distally and with full power of regeneration if a distal section of the nerve was made. Cajal also described and illustrated side branches and "collateral appendices" of fibers above the ligature on the twelfth day, with beadings of axis-cylinders approaching the constriction. Stroebe [14] also mentioned occasional collateral appendages of the axon above a complete compression lesion in the rabbit ear. Cajal assumed that these phenomena are regenerative. We ourselves have noted that on the twelfth day after a ligature which interrupts all fibers the region of the changes described by Cajal was completely necrotic. We assume, therefore, that the change presented by Cajal is in the fibers that escaped complete destruction at the level of ligature, a possibility that is difficult to prove in the mixed lesion produced by his loose ligature method, but which is obvious in the more uniform damage produced by our pressure clip. We regard the "regenerative phenomena" described by Cajal as identical with the reaction to edema and ischemia which we described, but exhibited over a shorter length of fiber than is a lesion produced by compression with a clip. In particular, the change described by Cajal as "reticulated appendices in sterile axons" (Cajal,[10] page 299) we observed to be associated with simple edema. He did not attempt to account for the absence of the apparatus of Perroncito, which we consider essential to the process of regeneration. We find that the essential feature of edematous change is, in fact, the lack of neurofibrillar condensation. The axon behaves simply as a fluid mass, which becomes greatly swollen and deformed. It is far from "sterile."

Only when necrosis of a segment of the axon occurred did neurofibrillar condensation (the phenomenon of Perroncito) and the sprouting of Perroncito spirals occur in the proximal segment. Comparison of the lesion of axis-cylinders of a nerve that has been clamped in a hemostat eight weeks previously and allowed to regenerate and that of an intermediate degree of pressure lesion produced by transitory compression with a tourniquet or clip and allowed to recover reveals many spirals of Perroncito in the former and the persistence of only edematous, irregular and altered nodes in the latter. This is further evidence of the fundamental difference in the regenerative process in the two types of lesion. Further, though in both types there is persistence of increase in endoneural cells and macrophages for a long period, the manner in which the flat endoneural cells surround the demyelinated segment of the intermediate type of pressure lesion is unique in our experience of lesions of peripheral nerve.

The small round cell with scant cytoplasm, apparently identical with the lymphocyte, appears throughout the nerve in response to trauma. With simple edema its margin is frequently notched; but there is scant cytoplasm, and no phagocytic activity is seen (figs. 3 *B* and *C* and 11 C). When the myelin gaps of the intermediate type of pressure lesion occur, similar cells with more cytoplasm are observed near each gap, with fat granules in the cytoplasm. When demyelination is extensive, there are greater numbers of such cells, each with a moderate amount of cytoplasm and irregularly shrunken nucleus. Only when wallerian degeneration occurs do

14. Stroebe, H.: Experimentelle Untersuchungen über Degeneration und Regeneration peripheren Nerven nach Verletzungen, Beitr. z. path. Anat. u. z. allg. Path. **13**: 160-278, 1893.

swollen, fat-laden gitter cells appear. They then seem to us to be merely a further transitional form of the same cells.

In our earlier paper on tourniquet lesion [3] we noted the close resemblance between this "intermediate degree of pressure lesion" and the "periaxial segmental neuritis" of Gombault,[15] which he noted in association with a variety of forms of peripheral neuritis. Gombault,[15] thus, first described a disorder of structure of the peripheral nerves distinct from wallerian degeneration. The effect of "periaxial neuritis" on conduction is unknown, for the circumstances of its production have always led to degeneration in more distal parts. In "periaxial neuritis" the loss of myelin occurs evenly over a whole segment, or parts of related segments. A small part so affected may resemble one of the bared nodes in our experiments, but the swollen myelin distal to a long stretch bared by ischemia is not seen in cases of periaxial neuritis. Nor are the coarse, fatty granules (Erzholz granules) in the lesions of periaxial neuritis caused by experimental lead intoxication (Stransky [16]) seen in the ischemic lesion. For these reasons, it appears preferable to regard ischemic demyelination as a new and distinct variety of disorder of the structure and function of the nerve fiber.

CONCLUSIONS

Compression of nerve by a metal clip exerting a tension of 170 to 430 Gm. for two hours induced transient paralysis lasting five to eighteen days. This paralysis was not associated with gross defect in sensation, and the distal portion of the nerve fibers did not degenerate. It was accompanied by intermittent loss of myelin at the nodes of Ranvier in the compressed area. The lesion was identical with the "intermediate degree of pressure lesion" induced by compression with tourniquet. Though recovery of motor conduction was early, the restitution of the myelin defect was only slightly advanced after six to eight weeks and was still defective after six months.

Continuous compression of a nerve by a metal clip exerting a tension of 5 to 7 Gm. did not interfere with conduction. The compressed segment was greatly narrowed, and the nerve was edematous on either side of the region of constriction. Striking histologic changes in myelin and axis-cylinder occurred in the edematous region. These changes appeared to be due to simple swelling of the myelin. They were associated with mobilization of the large pale endoneural cells.

Continuous compression by a 44 Gm. clip induced preservation necrosis of myelin and axis-cylinders under the clip, with edema and degeneration above and below the area of compression. The proximal degeneration was of the type due to excessive ischemia.

Continuous compression by clips exerting a tension of 9 or 10 Gm. induced delayed onset of motor paralysis on the fifth to the eighth day, which lasted up to twenty-five days, with rapid recovery and without necessarily any wallerian degeneration or change in nerve endings or muscle. The lesion was associated with segmental loss of myelin, as well as the changes recognized as related to edema. Restitution of myelin was gradually taking place six weeks after the beginning of the experiment. The demyelinated axis-cylinder stained poorly, if at all, with silver impregnation.

The effect of pressure on nerve is considered to be due entirely to ischemia, and the characteristic histologic lesion and dissociated paralysis form a distinctive type of neuropathologic reaction. The histologic evidence indicates that the dissociation between sensory and motor function is due to a functional property of the disorder of the axoplasm, and not to selective effect related to the size of the fiber.

The large flat endoneural cells surrounded the sheath of Schwann after demyelination.

818 Harrison Avenue.

15. Gombault, M.: Contribution à l'étude anatomique de la névrite parenchymateuse subaiguë et chronique; névrite segmentaire periaxile, Arch. de neurol. **1**:11-38, 1880.

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DYSTONIA

III. PATHOLOGY AND CONCLUSIONS

ERNST HERZ, M.D.

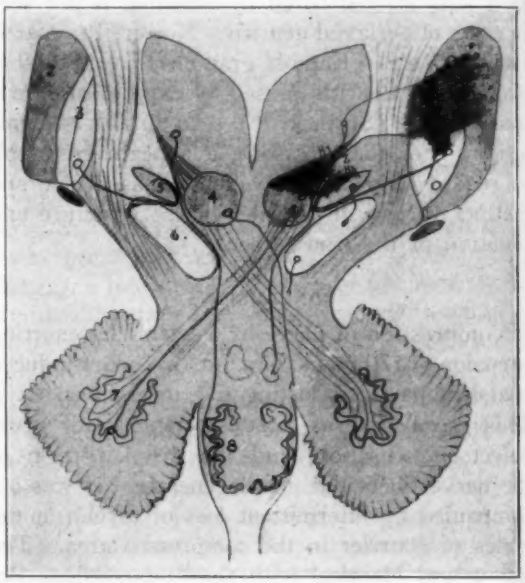
NEW YORK

The lesions which produce dystonic symptoms are encountered in the brain stem, particularly in the basal ganglia. In an earlier study [1] an attempt was made to compare the sites of lesions forming the basis of the various types of abnormal involuntary movements in nervous diseases. The lesions observed at autopsy in the cases in which dystonic symptoms were exhibited reported up to the time of publication of that report are shown in the figure. It is clear that one is far from being able to predict the exact site of the lesion from any given pattern of involuntary motor activity.

The present study, however, is concerned not so much with the site of the lesion as with the underlying pathologic process, since the peculiarity of the pathologic changes determines the type of onset and the course of the disease.

According to the fundamental investigations of C. and O. Vogt,[2] which have been confirmed by numerous studies and recently further elaborated and illustrated by Alexander,[3] the commonest disease processes affecting the basal ganglia may be differentiated as follows: (1) congenital malformations (status marmoratus and status dysmyelinisatus); (2) primary abiotrophy (status fibrosus), and (3) degenerative necrotizing processes (status disintegrationis), resulting from intoxication, inflammation, vascular lesions, mechanical trauma or nutritional deficiencies. The process of hepatolenticular degeneration (Wilson's disease) also is placed in this pathologic group.

In a review of all the cases with dystonic symptoms, those in which clinical analysis suggests the presence of necrotizing processes, with more or less localized lesions in certain parts of the brain stem, have already been separated. The syndromes seen in cases of status disintegrationis, resulting from intoxication, inflammation, vascular lesions, etc., have frequently been classified as symptomatic dystonia. It is perhaps preferable to designate the underlying etiologic factor and the pathologic changes to be expected and to speak, for instance, of encephalitis, carbon monoxide poisoning or birth injury with dystonic symptoms. Cases of this type can usually be recognized by a careful analysis of their clinical peculiarities.



Lesions observed in cases in which dystonic symptoms were exhibited. *1* is optic thalamus; *2*, putamen, with large and small cell; *3*, globus pallidus; *4*, red nucleus; *5*, corpus Luysi; *6*, substantia nigra; *7*, dentate nucleus, and *8*, olive.

Heavy shading shows the prevalent site of the lesions in the majority of cases.

The clinical characteristics of the remaining cases of dystonia were outlined in the last paper in this series. The present paper will be devoted to a review of the pathologic observations in the cases recognized clinically as those of dystonia. The clinical descriptions will first be analyzed in order to bring these cases in line with the suggested classification.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

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2. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. (supp.) **25**:627, 1919-1920.

3. Alexander, L.: The Fundamental Types of Histopathological Changes Encountered in Cases of Athetosis and Paralysis Agitans, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:334, 1942.

Data on Reported Cases of "Dystonia" with Pathologic Verification

Year	Author	Delivery *	Development *	Age of Onset, Yr.	Diagnosis	Clinical Group †	Pathologic Features	Anatomic Diagnosis
1918	Thomalla [4]	+	+	13	Torsion spasm	B	Softening in putamen	Wilson's disease
1920	Spiller [18]	..	+	5	Dystonia lenticularis	D	Lenticular nuclei reduced in size; worm-eaten appearance of putamen, loss of nerve cells, gliosis	Degenerative process
1921	Wimmer [5]	+	+	10	Torsion spasm	B	Destruction of nerve elements and proliferation of glia in striatum; cyst formation and necrosis	Wilson's disease
1922	Cassirer [14] (case 2)	..	+	7	Dystonia musculorum deformans	D	Edema of brain (agonal); diffuse changes of parenchyma, in striatum more than in cortex or thalamus	?
1923	Richter [19]	+	+	11	Torsion dystonia	D	Chronic progressive atrophy of large and small nerve cells of putamen; putamen reduced in size; few changes in pallidum, substantia innominata and substantia nigra	Degenerative process
1929	Marinesco and Nicolesco [20]	..	+	15	Contorsion dystonia	D	Chronic atrophy of small and large nerve cells in putamen and caudatum, with accumulation of lipid; gliosis; lipid in corpus Luysi; dilation of perivascular spaces	Degenerative process
1929	Laruelle and van Bogaert [15] AUTHOR: In study II development was abnormal.	..	—	At birth	Syndrome of rigidity with torsion spasm	D	Predominance of status dysmyelinisatus over atrophic process of nerve cells	Status dysmyelinisatus + atrophic process
1931	Lüthy [6]	..	..	18	Hepatolenticular degeneration, with torsion and athetoid movements	B	Severe changes in large cells of striatum, less in small cells; spotty demyelination; accumulation of iron and pseudocalcium pigments	Wilson's disease
1931	Dias [10]	..	Debility	10	Chronic epidemic encephalitis	B	Chronic process, particularly in cortex, substantia nigra and dentatum, less in striopallidum, corpus Luysi and cerebellar cortex	Chronic encephalitis
1932	Jakob [22] (case 1)	..	..	20	Torsion dystonia	D	Degenerative process with calcification in putamen, pallidum, lateral nucleus of thalamus, dentate nucleus, ganglia of pons and parts of cerebral cortex	Degenerative process
1932	Schmitt and Scholz [23]	..	+	22	Torsion dystonia	D	Pigment atrophy in striatum, pallidum, thalamus, dentate nucleus, nuclei of cranial nerves, olive and anterior horn cells; number of nerve cells (especially small cells) decreased in striatum; dilation of perivascular spaces; changes in pallidal cells, loss of fine myelin fibers	Degenerative process
1933	Foerster [13]	..	+	20	Torticollis spastica	D	Large lacunas in all lower levels of basal ganglia (état criblé)	?
1933	Davison and Goodhart [21] ... Case of Frauenthal and Rosenheck (J. Nerv. & Ment. Dis. 52 : 134, 1920)	+	+	7	Dystonia musculorum deformans	D	Shrinkage of left putamen and caudate nucleus; large cells, especially of putamen, decreased in number with changes; gliosis; poverty of striatal fibers; calcified vessels and deposits of iron in amygdaloid nucleus and corpus Luysi; fibers of neostriatum poorly stained; changes in some nuclei of cranial nerves and anterior horn cells	Degenerative process
1934	Guillain, Mollaret and Bertrand [7]	..	..	17	Postencephalitic torsion spasm	B	Changes in substantia nigra, large cells of striatum and cells of pallidum, diffuse lesions in central nervous system	Epidemic encephalitis
1934	Agostini [8]	..	..	10	Torsion spasm in epidemic encephalitis	B	Regressive changes of nerve elements, with little inflammatory reaction; circumscribed softening, due to circulatory changes; changes in cortex and substantia nigra; less severe alterations in lentiform and caudate nuclei and corpus Luysi; more severe changes in cerebellar cortex and dentate nucleus	Epidemic encephalitis

* In this table, the plus sign indicates normal delivery or development; the minus sign, abnormal delivery or development, and ..., no data.

† Group A consists of cases in which the report available was incomplete or the diagnosis unconfirmed; group B, cases of other well known diseases, and group D, cases of dystonia.

Data on Reported Cases of "Dystonia" with Pathologic Verification—Continued

Year	Author	Delivery	Development	Age of Onset, Yr.	Diagnosis	Clinical Group	Pathologic Features	Anatomic Diagnosis
1935	Munch-Petersen [11]	..	+	18	Torsion dystonia (?); diffuse encephalitis (?)	A	Chronic inflammatory condition, especially in cortex, ganglia of brain stem and thalamus; infiltration with rod cells; capillary infiltration with plasma cells and lymphocytes	Chronic inflammatory process
1936	van Bogaert and Scherer [12]	..	..	10	Torsion spasm	A	Systemic disease of pallidum and corpus Luysi; severe loss of ganglion cells, gliosis, loss of myelin sheaths, secondary degeneration of fibers of pallidum passing into corpus Luysi	?
1938	Davison and Goodhart [16]							
	Case 1	..	—	6 wk.	Dystonia musculorum deformans	D	Pronounced shrinkage of putamen and caudate nucleus; areas with deeply stained myelin fibers arranged in close bundles, numerous glia cells and fibers; ganglion cells decreased; cellular changes	Status marmoratus; degeneration of nerve cells
	Case 2	..	+	14	Dystonia musculorum deformans	D	Shrinkage of caudate nucleus, with decrease in number of cells and all types of cell changes; status marmoratus of upper pole of putamen; status dysmyelinisatus of inner segment of pallidum	Degenerative changes; areas of status marmoratus and dysmyelinisatus
	Case 3	..	+	8	Dystonia musculorum deformans	D	Shrinkage of putamen and caudate nucleus; large cells and a few small cells with signs of disintegration; status dysmyelinisatus of inner segment of pallidum and slight marble-like appearance of dorsolateral pole of putamen	Degenerative changes; status marmoratus and status dysmyelinisatus
	Case 4	..	+	7	Dystonia musculorum deformans	D	Shrinkage of putamen and caudate nucleus, with marble-like appearance of superior pole of putamen; large cells of putamen and caudate nucleus decreased in number and disintegrated; decrease of nerve cells in pallidum; cell changes in corpus Luysi and dentate nucleus	Degenerative changes; areas of status marmoratus
1939	Gordin [9]	..	..	+	.. Unilateral torsion dystonia	A	Slight rarefaction of large cells in caudate nucleus; obvious cell changes in putamen and pallidum; glia proliferation and increase in vessels, perivascular gliosis and capillary fibrosis	Epidemic encephalitis
1941	Nielsen [17]	+	..	18 mo.	Dystonia musculorum deformans	D	Putamens reduced in size; status marmoratus in both thalami; changes in putamens and dentate nuclei; lipid deposits; ganglion cells reduced in number	Degenerative changes; areas of status marmoratus
1942	Alexander [3]							
	Case 1	..	..	10 mo.	Torsion dystonia of trunk and neck; athetosis of tongue and face	D	.....	Status marmoratus
	Case 2	..	..	At birth	Bilateral athetosis; torsion dystonia shoulder girdle; opisthotonos of neck	D	.....	Status marmoratus of striatum; status dysmyelinisatus of pallidum
	Case 4	..	..	6 mo.	Athetosis of both arms; torsion dystonia of neck	D	.....	Status marmoratus

PRESENT INVESTIGATION

Pathologic studies were made in 26 cases of dystonia. In the table are indicated the significant clinical data and the pathologic observations. In 3 cases (Thomalla,[4] Wimmer [5] and Lüthy [6]) the softening process of Wilson's disease was observed. In 4 cases (Guillain, Mollaret and Bertrand,[7] Agostini,[8] Gordin [9] and Dias [10])

4. Thomalla, C.: Ein Fall von Torsionsspasmus mit Sectionsbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **41**:311, 1918.

5. Wimmer, A.: Etudes sur les syndromes extrapyramidaux: Spasme de torsion progressif infantile, Rev. neurol. **37**:952, 1921.

6. Lüthy, F.: Ueber die hepato-lentikuläre Degeneration, Deutsche Ztschr. f. Nervenh. **123**:101, 1931.

7. Guillain, G.; Mollaret, P., and Bertrand, I.: Etude clinique, cinématographique et anatomo-pathologique d'un grand spasme de torsion postencéphalitique, Rev. neurol. **1**:342, 1934.

(Footnotes continued on next page)

clinical and anatomic evidence of the process of chronic epidemic encephalitis was presented. The cerebral lesions in the case of Munch-Petersen [11] were probably also of a chronic inflammatory nature. The clinical description of the case of van Bogaert and Scherer [12] does not justify the diagnosis of dystonia. The report on the study of Foerster's case [13] is insufficient. Bielschowsky stated in a personal communication that the brain in Cassirer's case [14] was not particularly favorable to pathologic investigation, since agonal edema caused extensive parenchymatous changes and obscured the basic lesions.

Thus, of 26 cases, 15 are suitable for an approach to the question of the pathology of dystonia. The cases of Laruelle and van Bogaert,[15] Davison and Goodhart [16] (case 1), Nielsen [17] and Alexander [3] (cases 1, 2 and 3), 6 altogether, belong to the early form of the disease, the disease starting after delivery or in the first months of life. In the cases of Spiller,[18] Richter,[19] Marinesco and Nicolesco,[20] Davison and Goodhart [21] and Davison and Goodhart [16] (cases 2, 3 and 4) the first symptoms started between the ages of 5 and 15 years. These 7 cases belong to the juvenile type. In the cases of Jakob [22] (case 1) and of Schmitt and Scholz [23] the disease began at the ages of 20 and 22 years respectively. These 2 cases must be classified under the late type of the disease.

In the 6 cases of the early form, status marmoratus, alone or complicated by status dysmyelinisatus, was noted. In addition to the typical process of "marble anomaly," Laruelle and van Bogaert,[15] Nielsen [17] and Davison and Goodhart [16] (case 1) described an atrophic process of the nerve cells, whereas Alexander,[3] in his 3 cases of status marmoratus, noted that the nerve cells were completely normal as to number and size. Davison and Goodhart could even demonstrate the different degrees of deterioration of the nerve cell: ischemic changes, pallor with displaced nucleus, and pronounced destruction and disintegration. Accordingly, it must be assumed that, at least in a large number of cases of status marmoratus, cellular changes are clearly present in the form of progressive degeneration.

In the 2 cases of the late form a purely degenerative process of the nerve cells was observed. In addition, there were remarkable calcification in case 1 of Jakob [22] and accumulation of pigment in the case of Schmitt and Scholz.[23] The latter authors stressed "a close relationship with respect to histologic details and localization in Huntington's disease." The accumulation of lipids is uncommon; however, this has not been described in cases of Huntington's chorea, not even when the disease was of long duration.

Of the 7 cases of the juvenile form, in those of Spiller, Richter, Marinesco and Nicolesco and Davison and Goodhart,[21] a purely degenerative process was exhibited. The basal nuclei were reduced in size; there was apparent loss of nerve cells, and the remaining nerve cells were atrophic. Accumulation of lipids was noted in the case of Marinesco and Nicolesco. Calcified vessels and deposits of iron were present in the case of Davison and Goodhart.[21] In their 3 cases published in 1938, Davison and Goodhart [16] also demonstrated atrophic changes in the nerve cells; in addition, status marmoratus and, in 1 case, status dysmyelinisatus were noted in circum-

8. Agostini, C.: Sopra un caso di spasmo di torsione in encefalitica epidemica cronica (Nota clinica ed anatomo-patologica), Riv. di pat. nerv. **43**:440, 1934.

9. Gordin, R.: Case of Unilateral Torsion Dystonia: Clinico-Histologic Study, J. Nerv. & Ment. Dis. **90**: 344, 1939.

10. Dias, A. A.: Ueber einen Fall von chronischer Encephalitis mit eigenartigem klinischem und anatomischem Befund, Ztschr. f. d. ges. Neurol. u. Psychiat. **137**:82, 1931.

11. Munch-Petersen, C. J.: Beitrag zur Frage des pathologisch-anatomischen Substrats der Torsionsdystonie, Acta psychiat. et neurol. **10**:391, 1935.

12. van Bogaert, L., and Scherer, H. J.: Zur Frage der Beziehungen von Pallidum- und Kleinhirnläsionen zum Syndrom der Drehbewegungen um die Körperachse, Monatschr. f. Psychiat. u. Neurol. **93**:140, 1936.

13. Foerster, O.: Mobile Spasm of the Neck Muscles and Its Pathologic Basis, J. Comp. Neurol. **58**:725, 1933.

14. Cassirer, R.: Halsmuskelkrampf und Torsionsspasmus, Klin. Wchnschr. **1**:53, 1922.

15. Laruelle, L., and van Bogaert, L.: Etude anatomo-clinique d'un cas de syndrôme rigide, avec spasme de torsion, Rev. neurol. **1**:941, 1929.

16. Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: Clinicopathologic Study, Arch. Neurol. & Psychiat. **39**:939 (May) 1938.

17. Nielsen, J. M.: Autopsy in a Case of Dystonia Musculorum Deformans, Bull. Los Angeles Neurol. Soc. **6**:87, 1941.

18. Spiller, W. G.: Acquired Double Athetosis (Dystonia Lenticularis), Arch. Neurol. & Psychiat. **4**:370 (Oct.) 1920.

19. Richter, H.: Beiträg zur Klinik und pathologischen Anatomie der extrapyramidalen Bewegungsstörungen, Arch. f. Psychiat. **67**:226, 1923.

20. Marinesco, G., and Nicolesco, M.: Un cas anatomo-clinique de dystonie contorsive spasmodique avec lésions du striatum et des centres sous-thalamiques, Rev. neurol. **1**:973, 1929.

21. Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **29**:1108 (May) 1933.

22. Jakob, A.: Zur Frage der nosologischen und lokalisatorischen Auffassung der torsionsdystonischen Krankheitserscheinungen, Deutsche Ztschr. f. Nervenh. **124**:148, 1932.

23. Schmitt, W., and Scholz, W.: Klinischer und pathologisch-anatomischer Beitrag zur Torsionsdystonie, Deutsche Ztschr. f. Nervenh. **126**:53, 1932

scribed areas of the caudate nucleus, the putamen and the pallidum.

The most regular observation in all the cases of dystonia, except for the 3 cases studied by Alexander, was the degenerative cell change. Such alterations were most pronounced in cases of the late form and were predominant in cases of the juvenile form. In cases of the early form status marmoratus dominated the pathologic picture. An excess of myelinated fibers, although much less pronounced, was also seen in some cases of the juvenile form. This appears to mean that the slowly progressing abiotrophic process in itself causes the appearance of the progressive symptoms after a normal infancy, and sometimes a normal childhood and adolescence. If another factor which causes the "marble anomaly" is present as well, the progressive disease sets in at birth or in the first weeks of life.

In the differentiation of pathologic processes affecting the basal ganglia in dystonia, two factors must be considered. The process of primary abiotrophy is predominant; in addition, a malformation exists. The same factors, in potential form, might be responsible for the incompleteness of development, which is never remedied or compensated for after birth, and for the interruption of function and progressive deterioration of nerve cells in later life. The nature of these processes and the principles which determine them are not known. One can, therefore, describe only the pathologic changes and the clinical pictures connected with them.

COMMENT

When the results of clinical investigations previously reported are considered, together with the pathologic observations, one is in a better position to deal with the question: Can the condition designated as "dystonia" be regarded as a clinical and pathologic entity?

As has already been pointed out, insufficient clinical differentiation may obviously prevent a clear classification of cases with dystonic symptoms. Terminology is really not important. If, however, all cases in which dystonic symptoms occur are classified under "dystonia," confusion must result. The classification of a disease under a predetermined name results in some disregard of possible complexities in the situation, unless this name implies a distinct concept of all the facts, which eliminates any ambiguity. The diagnosis "dystonia" should, therefore, mean the same for each clinician and pathologist who uses the term.

In his most recent work, Keschner [24] stated that dystonia is a "symptom-complex which may be encountered in various pathologic conditions of the brain, caused by different etiologic factors." He distinguished between "idiopathic dystonia" and "symptomatic dystonia," but his evaluation of the pathologic changes did not refer to this clinical differentiation. This may be the reason that he designated the condition "merely as a variety of extrapyramidal disease whose motor disorder is predominantly dystonic in nature rather than a distinct clinical entity." This assumption of the existence of a large group of "extrapyramidal diseases" with certain variations seems a kind of renunciation, which does not take in account some remarkable facts elaborated in Keschner's own excellent report. The syndrome "parkinsonism" was found to be caused by different pathologic processes. Paralysis agitans, however, is a distinct clinical entity, characterized by clinical and pathologic peculiarities. Corresponding experiences with Huntington's chorea and Wilson's disease, to give two examples, demonstrate the possibility of establishing distinct clinical entities among the large group of extrapyramidal diseases. This, of course, should not conceal the fact that a large number of conditions, such as torticollis, tics, myoclonus and myorhythmias, cannot at present be attributed to distinct pathologic processes. Clinical and pathologic evidence in these conditions is far from conclusive. Accordingly, in case 15, described in part II of this series, with unusual symptoms, it seemed unwise to make any pathologic diagnosis, and the case was therefore classified under the heading "unknown progressive disease of early childhood with involuntary movements."

It might be of advantage to revise the demands for the establishment of an entity in clinical diagnosis. Originally, a disease entity was assumed to exist only if a distinct clinical constellation, including the cause, symptoms and course, corresponded with characteristic pathologic lesions. A certain combination of symptoms establishes a syndrome. During the course of a disease, however, the syndrome is characterized by more significant features. It may, for instance, appear in a pure form, or it may be framed by a more complex configuration of symptoms. The onset, course and development of neurologic signs and symptoms, together with a great number of other physical findings, make up the data which may be collected by clinical observation. The regular occurrence of various

24. Keschner, M.: Dyskinesias, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 10, p. 307.

peculiarities, the milieu in which the syndrome occurs, as much as the syndrome itself, enables one to establish it as a "clinical entity."

Pathologic investigations have established the existence of some fundamental processes of the nervous system. Purely degenerative processes of the nerve cells, processes with primary lesions of the vascular system, demyelinating processes, inflammatory processes, metabolic changes and involutional and senile changes may be distinguished as well recognizable groups. In some instances the localization of the peculiar lesions is of apparent regularity. Degenerative processes may be confined to the pyramidal or to the spinocerebellar system. Demyelinating processes occur almost exclusively in the white matter of the brain. In other instances the arrangement of lesions is strikingly characteristic, and almost pathognomonic. The histologic picture of dementia paralytica or of amaurotic familial idiocy as a whole is recognizable as the representation of a regularly occurring pathologic feature.

The diagnostic analysis of the underlying pathologic process, accordingly, has for its purpose, first, the definition of the characteristic combination of changes, and it has succeeded only in a few instances in establishing well circumscribed pathologic entities which are so characteristic that no doubt about their pathologic individuality can be raised.

In the establishment of a disease entity, the correlation of a clinical with a pathologic entity is an ideal demand which has not yet been fulfilled in the majority of instances. An example may illustrate the difficulties encountered, particularly with diseases of the basal ganglia. Huntington's chorea is a well established clinical entity. The psychic impairment, the choreic movements, the onset in middle age and the progressive course make a characteristic clinical picture. Study of the cerebral process revealed the characteristic degeneration of ganglion cells in the cortex, particularly in the caudate nucleus and the putamen. But further investigation revealed that the same cerebral process could be observed in cases in which the symptoms were quite different from the typical clinical picture of Huntington's chorea. Cases without psychic involvement were observed; in other cases a remarkable amount of stiffness, in addition to choreic movements, was present, and cases without hyperkinetic phenomena, but with exclusive occurrence of stiffness, and, finally, cases with dystonic symptoms, were noted. The clinician encounters symptomatic variations, but the pathologist notes a uniform disease process, not even always recognizably different in location. Accordingly, "Huntington's disease" is regarded as a term indicating a pathologic group, a distinct pathologic process underlying various clinical entities. The latter have characteristic clinical features in common, for instance, time of onset, course and development, and sometimes hereditary factors, but the symptoms may be quite different. The peculiarity of the pathologic process determines one part of the characteristics of the clinical entity—onset, course and hereditary transmission—while the symptoms may be of secondary importance in classification.

In this analysis dystonic symptoms, movements and postures, with a peculiar distribution of "excess of motion" and "excess of tension," have been described. These characteristic irregular, involuntary motor phenomena may be encountered in various conditions. Among these disturbances, a uniform group of cases with a selective appearance of dystonic symptoms and gradual development, without recognizable etiologic factors at onset, could be distinguished. These characteristics enable one to speak of the clinical entity "dystonia." In other cases a condition with different clinical characteristics, either following known etiologic factors, such as encephalitis, vascular diseases and tumor, or with additional symptoms not related to the specific involuntary motor activity, was differentiated from this clinical entity. As was previously explained, dystonia defined and circumscribed in this way is not simply a certain constellation of symptoms, a syndrome, but a clinical entity, with distinct clinical characteristics.

Already clinical experience permits the recognition of similarities between dystonia and other clinical entities. Early forms of dystonia resemble double athetosis in many respects. The onset of the first symptoms at or shortly after birth is significant in both conditions; the differentiation of the hyperkinetic phenomena in athetotic and in dystonic movements is sometimes difficult. Cases of the mixed type have been frequently reported, and Alexander, in considering only the early form of dystonia, expressed belief in the complete unity of these two clinical entities. The symptomatic differences between double athetosis and dystonia—in the juvenile and late forms more than in the early form—cannot be neglected, however. The course and development in cases of the late form of dystonia, and in some of the cases of the juvenile form, are not very different from the course and development of Huntington's chorea. In a few cases even the differentiation of the hyperkinesis may present difficulties; gradual onset of motor symptoms after normal development is common to both conditions. But in the majority of instances

there can be no doubt about the differences in the two clinical pictures.

The clinical reports of the cases in which pathologic investigation could be carried out were carefully studied and only the cases of dystonia selected. In the cases of late dystonia the lesions were of a purely degenerative nature; in addition, status marmoratus alone, or associated with status dysmyelinisatus, was found in cases of the early form. In the largest group of cases of dystonia, those of the juvenile form, degenerative changes of the nerve cells were predominant, in some cases combined with changes resembling those in status marmoratus, but of lesser intensity than in the early form of dystonia.

One has, therefore, to regard the primary process of abiotrophy as responsible for the symptoms in the great majority of cases. After a normal development over a period of years, a degenerative process develops, affecting groups of nerve cells of the basal ganglia. Presumably, the precise symptoms are due to involvement of specific circumscribed cellular systems—perhaps not confined to the recognizable gross structures of the basal ganglia. But this assumption has not yet been confirmed. The influence of constitutional, particularly hereditary, factors could not be strikingly demonstrated in the cases of dystonia here reported, although some cases of familial occurrence have been recorded.

SUMMARY

Dystonia defined by symptoms and by other clinical characteristics, such as the etiologic factors and the course and development, is a clinical entity. The underlying process in the basal ganglia must be attributed to degenerative abiotrophy of nerve cells in pure form or combined with status marmoratus and status dysmyelinisatus.

710 West One Hundred and Sixty-Eighth Street.

CEREBRAL THROMBOANGIITIS OBLITERANS

HISTOGENESIS OF EARLY LESIONS

I. MARK SCHEINKER, M.D.
CINCINNATI

Although the essential lesions of thromboangiitis obliterans in the peripheral blood vessels were described by Winiwarter as early as 1879 and have been studied since 1908 by Buerger and others, knowledge regarding the changes in the brain is incomplete. The occurrence of neurologic or psychiatric complications in the course of this vascular disease is well established by numerous clinical observations. It is surprising how few histopathologic studies concerning the cerebral changes are available. They are limited to a few observations by Spatz [1]; Straüssler, Friedmann and Scheinker [2]; Lindenberg,[3] and others. Several significant aspects of the disease remain obscure. The chronic stage of the vascular changes is confused by some investigators with certain types of rheumatic endarteritis (Bruetsch [4]); the acute lesions, with those of periarteritis nodosa. Little is known about the etiologic factors of the disease. One needs particularly to know more details of the early stage of the pathologic process.

This presentation is concerned with a detailed histopathologic study of changes in the brain in cases of thromboangiitis obliterans. Special attention is focused on the earliest manifestations of the pathologic process.

A representative case is chosen for report from the 3 cases of cerebral thromboangiitis obliterans that have reached this laboratory since 1937.

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1. Spatz, H.: Ueber die Beteiligung des Gehirns bei der v. Winiwarter-Buergerschen Krankheit (Thromboendangiitis obliterans), Deutsche Ztschr. f. Nervenh. **136**:86, 1935.

2. Sträussler, E.; Friedmann, R., and Scheinker, I. M.: Ueber die Endangiitis obliterans (v. Winiwarter-Buergersche Krankheit) unter besonderer Berücksichtigung der Hirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:155, 1937.

3. Lindenberg, R.: Ueber die Anatomie der cerebralen Form der Thromboendangiitis obliterans (v. Winiwarter-Buerger), Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:554, 1939.

4. Bruetsch, W. L.: Rheumatic Endarteritis of Cerebral Vessels: Sequel of Rheumatic Fever, Tr. Am. Neurol. A. **68**:17, 1942.

REPORT OF A CASE

A policeman aged 43, white, the father of 2 children, was admitted to the neurologic service of Cincinnati General Hospital on May 26. During the previous August, while in uniform, he had precipitously left for Florida without a word to his family or to his superior officers. As a result, he was suspended from his post and placed at a desk job, which he disliked.

About mid-November he began to have attacks which were described briefly as follows: (1) numbness extending from the elbow to the fingers or to the shoulder of either arm alone; (2) weakness of the right or of the left side of the face or of both sides, with slobbering and inability to talk or to swallow; (3) weakness of one or both sides of the face and, simultaneously, of the right upper extremity, or (4) dizziness and generalized weakness. When the face was involved, it became rigid and twitched, and the patient was unable to open or close his mouth; he had no control of the face or of the tongue; he could not speak, and he felt as though he had swallowed his uvula. When there was involve-

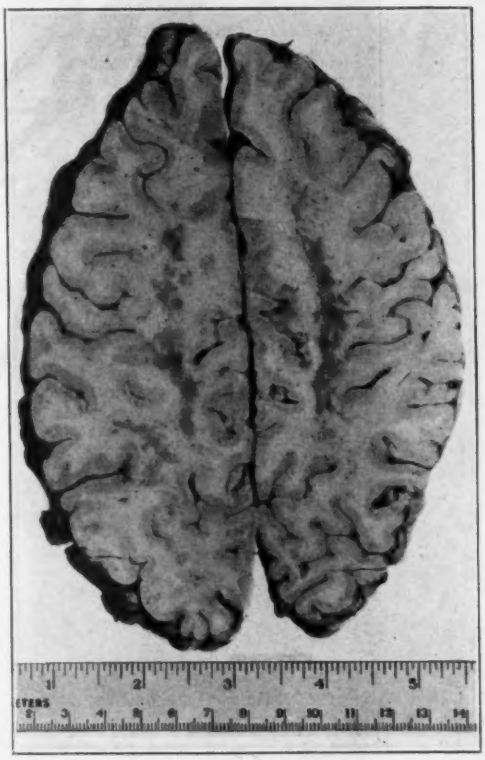

Fig. 1.—Diffusely scattered, small foci of softening, chiefly confined to the white matter of the centrum semiovale.

Fig. 2.—Far advanced proliferative changes of the intima, with formation of granulation tissue and almost complete occlusion of the lumen of the vessel. Cresyl violet stain; × 135.

Fig. 3.—Complete occlusion of a medium-sized vessel by a solid mass of connective tissue. Note the recanalization; the new-formed vessels are outlined with endothelial cells. Loyez stain; × 125.

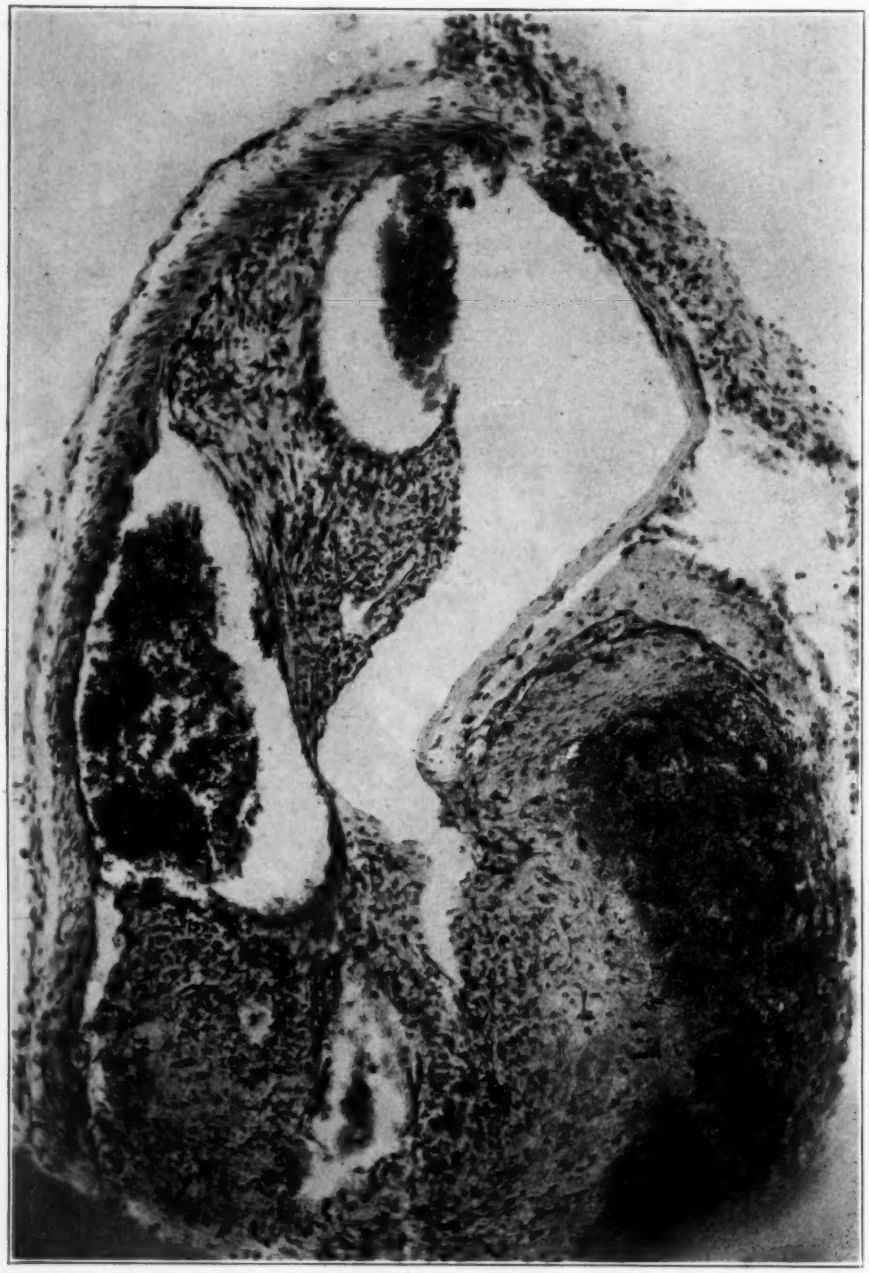

Fig. 4.—Occlusion of a large meningeal blood vessel by granulation tissue. Note the secondary thrombus formation, with large masses of coagulated blood. Cresyl violet stain; × 95.

ment of the right upper extremity, he was unable to release the grasp of the right hand. Numbness followed in whatever part was involved by the motor phenomena.

The attacks occurred as often as twice a week and as infrequently as once in three weeks. About fifteen minutes preceding an attack he noticed "twitching of one or the other eye," which resulted in diplopia. None of the attacks caused him to fall or to lose consciousness or to lose sphincter control. After the cessation of an attack he was completely fatigued and had to rest until strength returned. On May 24, two days before his admission to the hospital, weakness suddenly developed in his right extremities and progressed in forty-eight hours to complete paralysis, with accompanying aphasia.

Examination.—The weight was 210 pounds (95.2 Kg.); the temperature and the pulse and respiratory rates were normal; the blood pressure was 130 systolic and 80 diastolic. He had always been right handed. Abnormal neurologic signs were as follows: practically complete loss of ability to speak, his responses being confined to the answers, "all right" and "yeah"; bilateral ptosis; flaccid paralysis of the right limbs and the lower portion of the right side of the face; exhaustion of the abdominal and cremasteric reflexes on the right side, and greater activity of the deep reflexes on the right side than on the left. A weak Hoffmann sign was elicited on the right side; Babinski and Chaddock signs were obtained bilaterally, and Oppenheim and Gonda responses were present on the right side. He was alert and attempted to cooperate. He appreciated pinprick in all the extremities and over both sides of the face.

Course.—The first return of speech was profanity. On May 29 he began to answer questions slowly and sometimes whistled in response to questions. He was restless, yawned frequently, and was listless and drowsy at times. He gradually became more restless and noisy. The right extremities were noted to show increased resistance to passive movements on June 6. At that time he perseverated with the phrases or words that he had. The plantar responses remained bilaterally extensor throughout the course of the illness. On June 25 the temperature and the pulse and respiratory rates began to increase. The next day the patient appeared exhausted. Cheyne-Stokes respiration developed. He had vocal outbursts with perseveration until the morning of June 28. He became stuporous on June 29; at that time the temperature had reached 104.8 F. (rectal), the pulse rate 168 and the respiratory rate 60 a minute. He died on June 30, on the thirty-sixth day in the hospital.

Laboratory Data.—The blood pressure was 132 systolic and 94 diastolic nine years before admission, 130 systolic and 90 diastolic three years before and 140 systolic and 110 diastolic two months before. On examination at the time of admission, on May 26, the blood pressure was 130 systolic and 80 diastolic; on May 28, 150 systolic and 110 diastolic; on May 29, 130 systolic and 190 diastolic; on May 30, 150 systolic and 115 diastolic; on June 2, 150 systolic and 90 diastolic; on June 7, 150 systolic and 110 diastolic; on June 11, 145 systolic and 90 diastolic, and on June 15, 140 systolic and 90 diastolic. The Kahn and Wassermann tests of the blood, done repeatedly over nine years, gave negative reactions. An electrocardiogram, on June 1, was normal. Determinations of the visual fields, made on June 3, with imperfect cooperation, revealed no abnormality. Three analyses of the cerebrospinal fluid showed no abnormality except an increase in the total protein content, 46, 77 and 60 mg. per

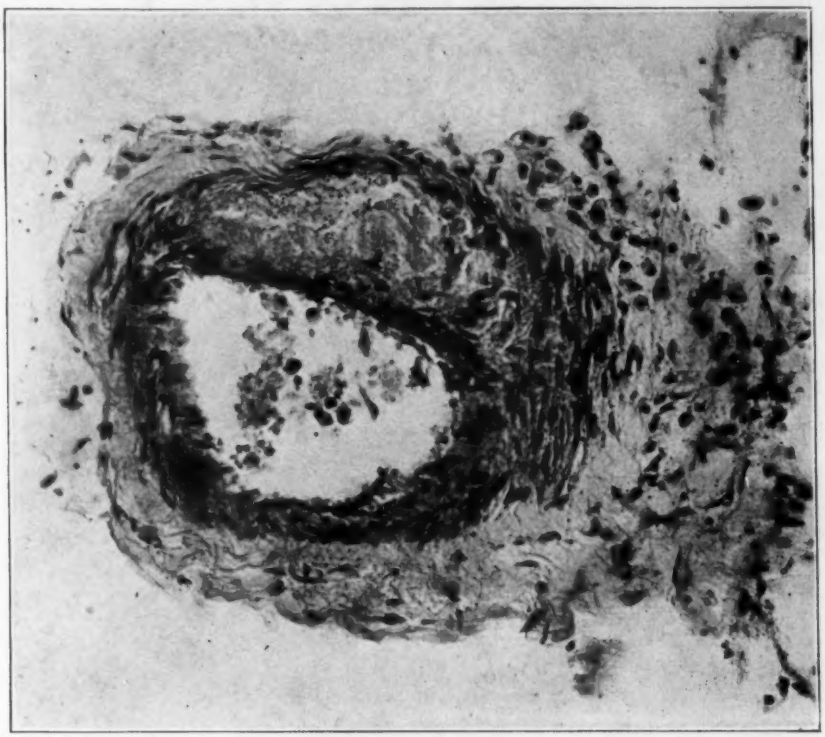

Fig. 5.—Early vascular lesions. A small artery with an intramural hemorrhage separates the intima from the muscularis. Cresyl violet stain; × 135.

Fig. 6.—Intramural hemorrhage in the stage of organization. The cellular proliferation of the intima and the presence of fibroblasts and macrophages in the area of hemorrhage are evident. Cresyl violet stain; × 125.

hundred cubic centimeters. The colloidal gold curves and the Wassermann reactions of the cerebrospinal fluid were normal. Roentgenograms of the skull, taken on May 29, and an encephalogram taken after injection of helium, on June 1, were normal. Three electroencephalograms were recorded: On March 31 a six lead monopolar study revealed no abnormality; on May 29 and June 12 six lead monopolar and eight lead bipolar studies showed diffuse, severe cerebral dysrhythmia.

Examination of the superior surface of the brain showed some fulness of the right cerebral hemisphere and diffuse thickening of the leptomeninges. There was a moderate degree of irregularity of the convolutions, caused by slight atrophy of some of the gyri, more pronounced in the left hemisphere than in the right. The blood vessels were grossly normal in appearance except for congestion of the smaller ones. Multiple coronal sections through the cerebral hemispheres, the cerebellum and the brain stem disclosed diffusely scattered, minute areas of softening, chiefly confined to the white matter of the centrum semiovale (fig. 1).

Microscopic Study.—The microscopic changes were essentially the same in all parts of the cerebrum, varying only in degree. There were lesions in the blood vessels and in the nerve tissue, those of the blood vessels being of two stages, necrobiotic and proliferative. The latter changes (figs. 2, 3 and 4) were characterized by an extensive proliferative process, confined to the inner layer of the vessel. The subendothelial part of the intima was enormously thickened because of the presence of a cellular granulation tissue, rich in fibroblasts. The tremendous thickening and hyperplasia of the intima led to considerable narrowing of the lumen of the vessel, with partial or total occlusion. The proliferative changes involved as a rule the entire intima, and in some of the larger vessels they were associated with secondary thrombus formation. The latter probably was the result of the degenerative changes frequently observed within the endothelial layer of the intima. In blood vessels in which the intimal proliferation was not far advanced the endothelial layer was fairly well preserved; in vessels with more advanced lesions the entire intima appeared to be transformed into a strip of connective tissue. In the vessels which disclosed signs of recanalization the newly formed lumens were outlined with endothelium (fig. 3). No lesions other than these intimal changes were observed in the vessel walls. The elastic membrane was usually preserved. Only in those vessels with far advanced proliferative changes of the intima did the elastic membrane occasionally show a moderate degree of atrophy and degeneration. The muscularis usually remained intact except in vessels presenting extreme changes, in which this layer had undergone atrophy and degeneration. As a rule, the adventitia was not affected; occasionally it was only slightly hyperplastic. It is to be emphasized that there were no inflammatory changes within or about the vessels. The vascular lesions were confined mostly to the medium-sized pial veins and smaller arteries. Larger blood vessels and capillaries usually were not affected.

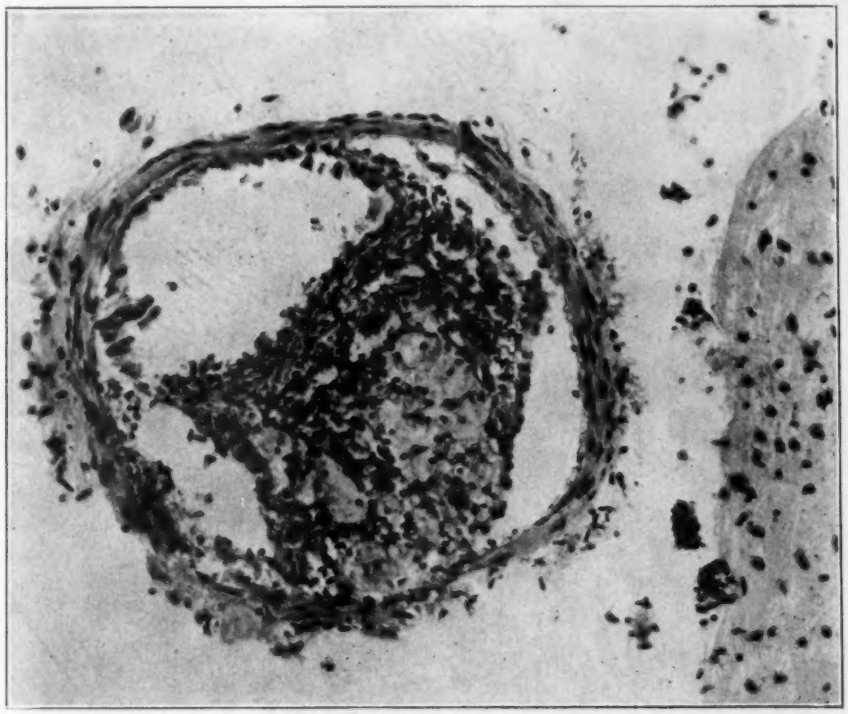

Fig. 7.—Intramural hemorrhage in an advanced stage of organization, showing the cellularity of the subendothelial tissue and the considerable narrowing of the lumen of the vessel.

In some of the early vascular lesions it seemed possible to trace the morbid process from its beginning. The early changes (figs. 5, 6, 7 and 8) appear to cast light on the pathogenesis of the vascular lesions. Figure 5 shows a small artery containing an intramural hemorrhage, which separated the coats of the vessels. The lining endothelium was swollen and protruded into the lumen of the vessel. The intramural bleeding was confined to the subendothelial tissue and the muscularis. The cells of the subendothelial part of the intima had undergone complete necrosis. The muscularis was somewhat changed, and its nuclei were swollen or

Fig. 8.—A meningeal blood vessel with a solid mass of granulation tissue. A large area of softening lies in the adjacent gray matter. Cresyl violet stain; × 95.

Fig. 9.—Necrosis and rarefaction of nerve tissue about a thrombosed vein. Hematoxylin-eosin stain; × 125.

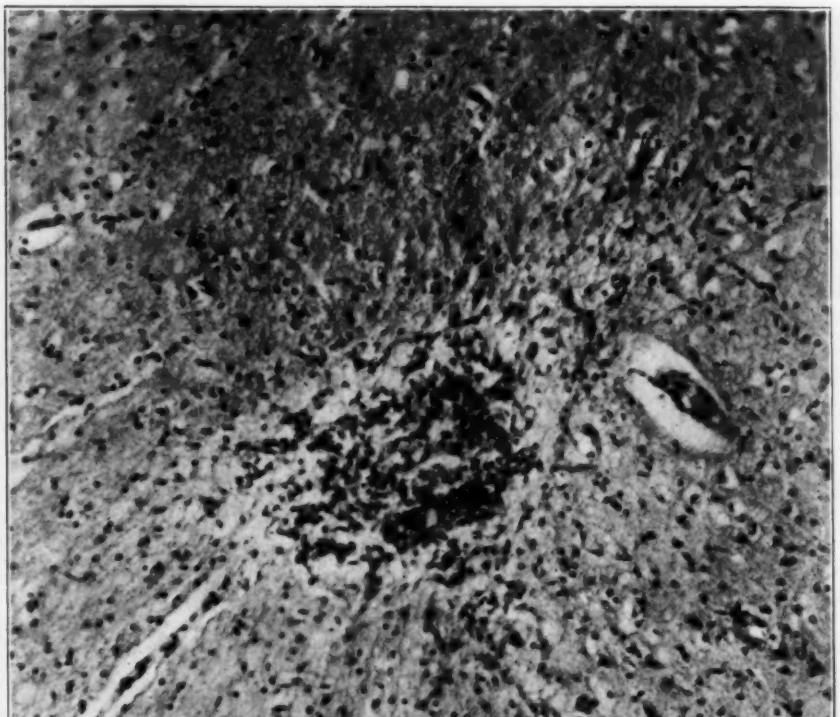

Fig. 10.—Circumscribed area of glial scar formation. Cresyl violet stain; × 125.

slightly disintegrated. The adventitia usually was preserved. Figures 6 and 7 illustrate the progress of the process. The extravasated blood had been absorbed, and the necrobiotic changes of the subendothelial tissue were followed by a reactive cellular proliferation, chiefly fibroblastic. Comparison of this stage of intimal proliferation with that of the later stages revealed the following discrepancy: Whereas in the older lesions there were advanced scar formations in the form of fibrosis, the earlier changes were characterized by cellularity and the absence of proliferation of connective tissue fibers. In the earlier lesions the subendothelial part of the intima was rarefied and reticulated and contained numerous proliferated, swollen fibroblasts and histiocytes. The latter were usually filled with blood pigment. The lumens of the vessels were narrowed by the swollen endothelium. Figure 8 illustrates a more advanced stage of intimal proliferation, in which the subendothelial tissue was dense and there was beginning proliferation of connective tissue fibrils. This stage approached the final phase, that of scar formation, which is illustrated in figures 3 and 4.

Three types of focal lesions of the nerve tissue were observed: (1) diffusely scattered areas of softening, characterized by the presence of a large number of fat granule cells (fig. 8); (2) tissue rarefaction, representing an early stage of disintegration of nerve tissue, without reactive glial changes (fig. 9), and (3) small, circumscribed areas of glial scar formation (fig. 10).

All three types of focal lesions have in common alterations of the blood supply by the narrowing or complete occlusion of the lumen of the vessels. Their differences might be explained by variations in the rapidity and completeness of the circulatory disturbance and by the caliber of the damaged blood vessel.

The lesions in the nervous system may be summarized as follows: There was widely disseminated focal destruction of tissue, dependent on alteration of the blood supply, which was the result of narrowing of the vessel lumen, with partial or complete occlusion. The vascular process may be divided into two stages, early necrobiotic and late proliferative changes. It is reasonable to assume that the process begins with intramural hemorrhage. The extravasated blood produces a secondary proliferative reaction of the subendothelial part of the intima. The latter becomes tremendously thickened and leads to narrowing of the vascular lumen. The endothelial lining of the intima degenerates, and secondary thrombus formation occurs, with complete occlusion of the lumen of the vessel. A progressive destruction of the adjacent nerve tissue results.

COMMENT

In the past most attention has been devoted to the far advanced intimal proliferation, resulting in vascular occlusion. These changes, it is thought, should be considered as relatively far advanced, old lesions, by which the vessel wall has become secondarily changed. From a pathogenic point of view, study of the earliest stages of the vascular change appears to be of greater significance. The most frequently observed early vascular alteration was the formation of small intramural hemorrhages. The innermost part of the media appeared frayed into several thin laminas. The interlamellar spaces harbored red blood cells, macrophages and serous fluid (figures 5, 6, 7 and 8). With further advance of this necrobiotic process, a reactive cellular proliferation of the subendothelial connective tissue took place. The subendothelial tissue at this stage appeared cellular and contained numerous proliferated and swollen fibroblasts and histiocytes; the latter harbored large masses of blood pigment. These changes were followed by the commonly described, final, stage of proliferation of connective tissue fibrils, resulting in scar formation and occlusion.

One may only speculate on the nature of these early vascular lesions. The intramural hemorrhage might be considered to be associated with functional vascular disturbances (possibly of the angiospastic and vasoparalytic type), of prolonged duration and repeated occurrence. The earlier clinical signs of the cerebral form of thromboangiitis obliterans are manifest as signs of transient focal lesions, such as transient palsy, numbness, speech disturbance and episodes of unconsciousness. These fluctuating clinical symptoms appear to be the result of disturbances of the cerebral circulation, which usually are reversible rather than permanent.

It is reasonable to suppose that reversible circulatory disturbances of repeated occurrence may precede permanent vascular change. The intramural hemorrhage might be a precursor, or even a catalyst, of the fixed lesion.

Foerster and Guttmann [5] observed transient vasospastic phenomena of the retinal arteries ophthalmoscopically in a typical case of thromboangiitis obliterans.

SUMMARY

In this morphologic study of the vascular alterations in the brain associated with thromboangiitis obliterans, the occurrence of small intramural hemorrhages is considered to be the earliest vascular change.

Cincinnati General Hospital.

5. Foerster, O., and Guttmann, L.: Cerebral Komplikationen bei Thromboangiitis obliterans, Arch.f. Psychiat. **100**:506, 1933.

THE ELECTROENCEPHALOGRAM OF CRIMINALS

ANALYSIS OF FOUR HUNDRED AND ELEVEN CASES

DANIEL SILVERMAN, M.D.
Assistant Surgeon (Reserve) United States Public Health Service
SPRINGFIELD, MO.

The tendency to view certain types of criminals as neuropsychiatric problems brings into focus the importance of a consideration of abnormalities of the central nervous system, as well as psychogenic factors. Electroencephalography seems to be an effective method of detecting many such abnormalities. The purpose of this communication is to report and interpret the electroencephalographic observations on 411 male criminals at the Medical Center for Federal Prisoners.

MATERIAL AND METHODS

Criminologic and sociologic data on the prisoners are given in tables 1, 2 and 3, and their residential distribution is shown in figure 1.

Clinically, the prisoners were classified under four large categories: psychopathic states (208 men), psychoses (80 men), normal mental status (60 men) and abnormalities of the central nervous system (63 men). The last group was included solely as a check on the competence of the technic employed in detecting abnormalities of the brain by the electroencephalogram; the distributions of the organic conditions were: neurosyphilis, 21 men; epilepsy, 31 men; post-traumatic encephalopathy, 6 men; alcoholic psychosis with deterioration, 3 men; multiple sclerosis with cerebral involvement, 1 man, and ill defined disease of the nervous system, 1 man. Except in the psychopathic group and the group with organic abnormalities of the central nervous system, the men incarcerated for violation of the Selective Service law were excluded. The distribution of the group with psychoses was as follows: dementia precox, 50 men (62.5 per cent); psychosis with psychopathic personality, 10 men (12.5 per cent); psychosis with mental deficiency, 7 men (8.7 per cent); paranoia and paranoid conditions, 5 men (6.3 per cent); manic-depressive psychosis, 2 men (2.5 per cent), and psychosis, undiagnosed type, 6 men (7.5 per cent). A normal control series consisted of 60 volunteers from the personnel and from a nearby Army post.

Electroencephalograms were taken with a five channel, ink-recording electroencephalograph. Placement of twenty-two electrodes over the prefrontal, frontal, central or motor, parietal and occipital areas of the scalp, for both monopolar and bipolar leads, was used routinely. Tracings from each hemisphere and simultaneous recordings from homologous areas of the two hemispheres, according to a technic previously outlined,[1] were made with the patient in a supine position in a semidarkened, partly sound-proofed room. Each test included a two minute period of hyperventilation, and the minimum total recording time was eighteen minutes. Records were classified as normal, borderline abnormal and abnormal.[1] Examples of each type are given in figure 2.

From the United States Public Health Service, Medical Center for Federal Prisoners.

ELECTROENCEPHALOGRAPHIC OBSERVATIONS

The percentage of abnormalities in the group with organic disease was expectedly high (table 4). Of the 31 epileptic subjects, the electroencephalograms of 26 were abnormal; those of 3 were borderline abnormal, and those of 2, normal. This result is in accord with studies of noncriminal epileptic patients[2]; however, the infrequency of fast and spike potentials (4 patients) and of the "petit mal" slow wave and spike formation (3 patients) was surprising. The most common abnormality (15 patients) was a bilaterally synchronous 6 per second delta rhythm. The correlation between the clinical estimate of the degree of damage to the brain and the percentages of electroencephalographic abnormalities is illustrated by 21 subjects with neurosyphilis. Six of these prisoners were suffering from dementia paralytica or the tabetic form of the disease; all gave evidence of intellectual impairment, and all had abnormal electroencephalograms. Seven had minimal signs of cerebral involvement; of these, 2 had an abnormal, 2 a borderline and 3 a normal electroencephalogram. Eight were considered to have asymptomatic neurosyphilis (pathologic changes in the spinal fluid only); of these, 2 had an abnormal, 1 a borderline and 5 a normal electroencephalogram.

The psychopathic prisoners were closely similar to the prisoners with organic disease in the frequency (75 per cent) of borderline and ab-

1. Silverman, D.: Clinical and Electroencephalographic Studies on Criminal Psychopaths, Arch. Neurol. & Psychiat. **50**:18-33 (July) 1943.

2. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111-128 (Aug.) 1943.

TABLE 1.—*Offenses Committed by Four Hundred and Eleven Prisoners*

	Homosexual Psychopaths	All Psychopaths	Prisoners with "Organic" Disease of Brain: Psychotic Prisoners	Prisoners with "Organic" Disease of Brain: Normal Prisoners	All Prisoners: Number	All Prisoners: Per Cent
1. Crimes of acquisition, without violence	..	..	..	..	285	69.3
A. Thefts	..	..	..	..	179	43.5
Automobile	0	87	11	15	124	
Interstate shipment	0	6	3	1	12	
Mail and postoffice	0	16	5	5	27	
Other types	0	9	4	2	16	
B. Swindles	..	..	..	..	56	13.6
Embezzlement and mail fraud	0	2	3	5	13	
Counterfeiting	0	2	4	2	15	
Forgery	0	6	1	3	13	
Impersonation	0	7	0	5	15	
C. Illicit business	..	..	..	..	50	12.2
Liquor	0	2	12	7	34	
Narcotics	0	0	4	1	10	
White slave traffic	0	3	0	0	6	
2. Crimes involving violence, actual or implied	..	..	..	..	97	23.6
A. For money	..	..	..	..	30	7.3
Bank robbery	0	1	5	0	7	
Other robbery	0	3	2	1	6	
Kidnapping and extortion	0	6	10	0	17	
B. Not for money	..	..	..	..	17	4.1
Assault	0	2	2	1	7	
Homicide	0	0	6	0	7	
Threatening letters	0	1	0	1	3	
C. Sexual	..	..	..	..	50	12.2
Sodomy	29	4	1	0	34	
Rape	0	4	0	0	4	
Violation of Mann Act	0	1	1	7	9	
Obscene letters	0	1	2	0	3	
3. Miscellaneous	..	..	..	..	29	7.1
Selective service violation	4	10	1	5	20	
Other offenses	1	1	4	1	9	

TABLE 2.—*Previous Criminal Records*

	Psychopaths: Homosexual Group		Psychopaths: Nonhomosexual Group		All Psychopaths		Psychotic Prisoners		Prisoners with "Organic" Disease		Normal Prisoners		All Prisoners	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No previous record	29	85.3	12	6.9	41	19.7	16	20.0	20	31.8	14	23.3	91	22.2
Minor record	2	5.9	34	19.5	36	17.3	10	12.5	9	14.3	8	13.3	63	15.3
One reformatory* or penitentiary incarceration	3	8.8	47	27.0	50	24.0	18	22.5	21	33.4	16	26.7	105	25.5
Two major penal incarcerations	0	0.0	51	29.3	51	24.5	17	21.2	6	9.4	12	20.0	86	20.9
More than two incarcerations	0	0.0	30	17.2	30	14.4	19	23.8	7	11.1	10	16.7	66	16.1

* Five or more jail sentences were arbitrarily called equivalent to one penitentiary experience.

TABLE 3.—*Age Distributions*

Age Group, Yr.	Normal Controls: No.	Normal Controls: Percentage	Normal Prisoners: No.	Normal Prisoners: Percentage	Psychopaths: No.	Psychopaths: Percentage	Psychotic Prisoners: No.	Psychotic Prisoners: Percentage	Prisoners with Organic Disease of Brain: No.	Prisoners with Organic Disease of Brain: Percentage	Total: No.	Total: Percentage
16-19	0	0.0	4	6.6	43	20.7	3	3.8	2	3.2	52	11.0
20-24	10	16.7	5	8.3	89	42.8	10	12.5	21	33.3	135	28.6
25-29	13	21.6	7	11.7	48	23.0	15	18.7	11	17.5	94	20.0
30-34	18	30.0	14	23.4	15	7.2	9	11.3	7	11.1	63	13.4
35-39	10	16.7	19	31.7	4	1.9	15	18.7	14	22.2	62	13.2
40-44	7	11.7	5	8.3	5	2.4	13	16.3	5	7.9	35	7.4
45-49	2	3.3	4	6.6	0	0.0	7	8.7	2	3.2	15	3.2
50 and over	0	0.0	2	3.3	4	1.9	8	10.0	1	1.6	15	3.2
Total	60		60		208		80		63		471	
Median ages	32		34		22		36		27		27	

normal electroencephalograms (table 4). The types of abnormalities encountered have been described previously [1]; the most common abnormality was a 6 per second delta rhythm, seen chiefly in the frontal and central leads. For purposes of this study, the psychopathic prisoners were separated into four groups: the hostile, the hedonistic, the inadequate and the homosexual. The homosexual criminals in this classification were considered free from other manifestations of psychopathic aberration; almost all were sexual offenders from the Army, and few had been arrested previously (table 2). Pathologic electroencephalograms were more frequent among the hostile and hedonistic groups (80 per cent) than among the inadequate (67.4 per cent) or the homosexual group (67.7 per cent).

TABLE 4.—*Electroencephalographic Classification*

	Electroencephalogram					
	Normal		Borderline		Abnormal	
	No.	%	No.	%	No.	%
Psychopaths	52	25.0	48	23.1	108	51.9
Hostile	13	20.0	16	24.6	36	55.4
Hedonistic	12	20.0	16	26.6	32	53.4
Inadequate	16	32.6	10	20.4	23	47.0
Homosexual	11	32.3	6	17.7	17	50.0
Psychotic prisoners, all	44	55.0	17	21.2	19	23.8
Dementia precox	31	62.0	11	22.0	8	16.0
Other psychoses	13	43.3	6	20.0	11	36.7
Normal prisoners	44	73.3	9	15.0	7	11.7
Prisoners with "organic" disease of brain	11	17.5	10	15.8	42	66.7
Epilepsy	2	6.5	3	9.7	26	83.8
Other disease	9	28.2	7	21.8	16	50.0
Normal controls	51	85.0	6	10.0	3	5.0

Fig. 1.—Residential distribution of offenders.

The inclusion of psychopathic psychotic criminals in the psychotic group was partly responsible for the high percentage of abnormalities (table 4; 45 per cent). In the largest group of psychotic patients, those with schizophrenia, the electroencephalograms of 31 (62 per cent) were normal; those of 11 (22 per cent) were borderline, and those of 8 (16 per cent) were abnormal. This is similar to the distribution of abnormalities found in civilian schizophrenic patients.[3]

Cursory neuropsychiatric examinations could not be expected to detect the less obvious psychopathic conditions among the "normal" criminals, and this fact may account for the larger percentage of electroencephalographic abnormalities in this group (26.7 per cent), as compared with that for the control, or personnel, group (15 per cent). Recidivism had no apparent relation to the presence of an abnormal electroencephalogram.

In the control group, 3 (5 per cent) had abnormal electroencephalograms and 6 (10 per cent) borderline abnormal electroencephalograms. Careful anamnesis for factors that may have been responsible for these abnormalities, e. g., familial epilepsy, probable birth injuries, encephalopathy due to infection or trauma in childhood or neurologic disease, revealed positive evidence for 8 of the 9 subjects. Such findings corroborate the contention [4] that a carefully selected group of normal subjects is likely to have an almost 100 per cent incidence of normal electroencephalograms.

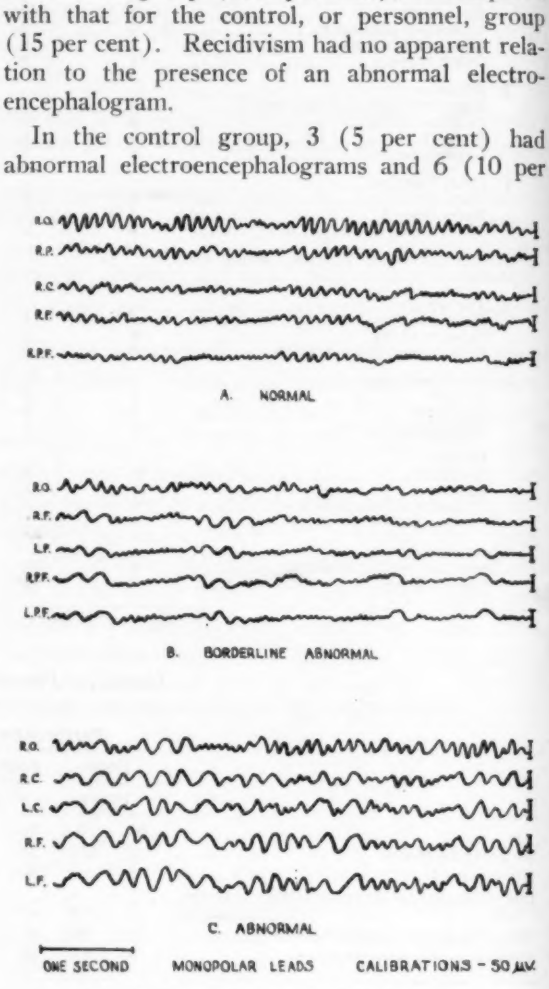

Fig. 2.—Sample electroencephalograms.

COMMENT

The electroencephalographic data are arranged in figure 3 to illustrate the progressive frequency

3. Finley, K. H., and Campbell, C. M.: Electroencephalography in Schizophrenia, Am. J. Psychiat. **98**:374-381, 1941.

4. Williams, D.: The Significance of an Abnormal Electroencephalogram, J. Neurol. & Psychiat. **4**:257-268, 1941.

of electroencephalographic abnormalities from normal controls to patients with organic disease. If psychopaths could have been excluded from the normal criminal group, the percentages in figure 3 would indicate that the electroencephalogram is not more abnormal for normal criminals than for normal civilian controls. Therefore, it would seem that the electroencephalogram cannot be considered a significant aid in the diagnosis of the source of criminalism. Several important differences between criminal and noncriminal psychotic patients were found in a previous study,[5] and it was thought that the electroencephalogram might help in explaining these differences. However, as already stated, pathologic electroencephalograms were no more frequent

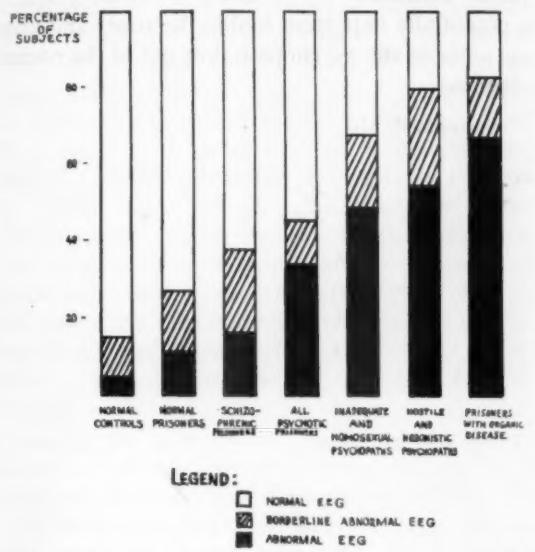

Fig. 3.—Graph showing relation of frequency of abnormal electroencephalograms to the criminal groups and to normal controls. Normal electroencephalograms are indicated by plain areas; borderline abnormal electroencephalograms, by cross-hatched areas, and abnormal electroencephalograms, by black areas.

among psychotic criminals than among civilian psychotic patients. Unquestionably, however, the electroencephalogram is vitally important in the study of psychopathic criminals, especially the hostile and the hedonistic type, who exhibit cerebral dysrhythmia. Hill and Watterson [6] observed that 32 per cent of inadequate and 65 per cent of aggressive psychopaths have abnormal electroencephalograms, and Knott and Gottlieb [7] reported an incidence of from 41 to 72 per cent of abnormalities among the psychopaths in their series.

Two hypotheses concerning the nature of the cerebral disorder have been suggested: (1) Psychopathy bears a close relation to epilepsy [8]; and (2) the psychopath's brain, as well as his personality,[9] is immature. In support of the latter idea, Hill and Watterson [6] pointed out that the normal slow alpha activity of childhood is considered equivalent to pathologic delta activity when it is found in late adolescence or in adult life. This suggests the possibility that the psychopath's abnormal electroencephalogram may eventually "mature" and become normal. To test the validity of this assumption, the electroencephalograms of psychopaths were arranged according to age groups (table 5). It may be seen that there is a tendency to fewer abnormalities in the electroencephalogram as age increases.

TABLE 5.—*Relation of Age and Electroencephalogram of Psychopathic Criminals*

	Electroencephalogram					
	Normal		Borderline		Abnormal	
Age Group, Yr.	No.	%	No.	%	No.	%
16-19	8	18.7	10	23.2	25	58.2
20-24	23	25.9	21	23.6	45	50.5
25-29	13	27.1	10	20.8	25	52.1
30 and over	8	28.5	7	25.0	13	46.4

The final answer cannot be determined until subsequent clinical and electroencephalographic studies of the present psychopathic children and young adults are made in adult or in later adult life. The theory of "immaturity" is not incompatible with organic disease of the brain or with epilepsy. It is well known [10] that some epileptic patients, especially adolescents, tend to improve—that seizures become less frequent, and may even cease (compare electroencephalographic studies of pyknolepsy [11]). Gibbs [2] found fewer electro-

5. Silverman, D.: Psychoses in Criminals: A Study of Five Hundred Psychotic Prisoners, J. Crim. Psychopath. **4**:703-730, 1943.

6. Hill, D., and Watterson, D.: Electroencephalographic Studies of Psychopathic Personalities, J. Neurol. & Psychiat. **5**:47, 1942; abstracted, Arch. Neurol. & Psychiat. **49**:916 (June) 1943.

7. Knott, J. R., and Gottlieb, J. S.: The Electroencephalogram in Psychopathic Personalities, Psychosom. Med. **5**:139-141, 1943.

8. Silverman, D.: The Electroencephalogram and Therapy of Criminal Psychopaths, J. Crim. Psychopath. **5**:439, 1944. Gibbs [2] presented the concept that the abnormal brain wave is an indication of "epileptogenicity" rather than of "organicity."

9. Mangun, C. W.: The Psychopathic Criminal, J. Crim. Psychopath. **4**:117-127, 1942.

10. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, pp. 27, 481 and 482.

11. Owen, J. W., and Berlinrood, L.: Clinical and Electroencephalographic Studies in Pyknolepsy, Am. J. Psychiat. **98**:757-766, 1942.

encephalographic abnormalities in epileptic adults than in epileptic children. The promise that psychopaths may in later years improve, and even "recover," is not generally accepted. No one knows what becomes of the youthful psychopaths. Some die of violence or in the electric chair; others receive long sentences and are taken "out of circulation"; some become the more astute swindlers, and some, the middle-aged recidivists, who pass as "normal" criminals. It is conceivable that some recover sufficiently to lead a relatively normal and law-abiding existence.

The psychopath has a disruptive effect on the life of the reformatory and prison, exercises a malevolent influence on other inmates, invites severe disciplinary measures, from which he benefits little, and on his release commits more, and often more violent, crimes. In a recent study of 30 men convicted of murder,[12] 17 were psychopaths with previous criminal records. The severe personality disturbance and electroencephalographic abnormalities make it imperative that psychopaths receive a specialized approach and handling. Certainly, existing methods are inadequate; psychopaths are discharged at expiration of their sentences with full knowledge that no "cure" or "rehabilitation" has been effected and that they represent a potential menace to society.

12. Rosanoff, A. J.: Thirty Condemned Men, Am. J. Psychiat. **99**:484-495, 1943.

SUMMARY

In a study of the electroencephalograms of 411 prisoners, including "normal" criminals, psychotic and psychopathic criminals and offenders with "organic" disease, the most significant observation was the high percentage (75) of borderline and abnormal patterns among the psychopathic criminals. The electroencephalograph is a potentially important tool in the study and management of the psychopath, but not of the normal criminal.

Springfield, Mo.

VASOPARALYSIS OF THE CENTRAL NERVOUS SYSTEM, A CHARACTERISTIC VASCULAR SYNDROME

SIGNIFICANCE IN THE PATHOLOGY OF THE CENTRAL NERVOUS SYSTEM

I. MARK SCHEINKER, M.D.
CINCINNATI

Detailed descriptions of the histologic features of vascular disturbances of the central nervous system are scarce. This may be because of a common misconception that many of the vascular changes observed in the central nervous system are "functional," and therefore "without anatomic basis." Of course what is meant is that a certain type of vascular alteration, though structural, may be reversible; the actual changes are often so minimal that it may be difficult to demonstrate them in fixed tissue. Any one, however, should recognize that a change in size of a vessel is a structural or a morphologic change. Possibly because of this loose concept of "functional" vascular changes, the histopathologically visible evidence of the alteration that remains is often overlooked; certainly, not much importance has been assigned to it. In this paper this particular vascular change will be described, and meaningless discussion as to whether it is "functional or organic" will be omitted.

During the past years I have had the opportunity to observe histopathologic lesions in a large number of cases of cerebral edema,[1] in which vascular alterations are the most significant and characteristic feature. In a recent study[2] of the lesions of the central nervous system following trauma such changes were predominant.

The frequent occurrence of vascular disturbances suggests the advantages that would accrue if their morphology and pathogenesis were better known. The purpose of this presentation is to describe the characteristic pathologic syndrome of vasoparalysis of the central nervous system and to indicate a possible mechanism for its occurrence. This paper is the result of a study of a large number of cases, some of which have been described elsewhere.[2] Two typical and illustrative cases serve as a point of departure.

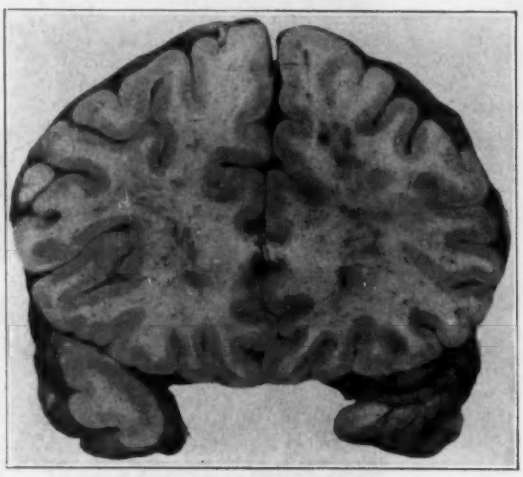

Fig. 1 (case 1).—Petechial hemorrhages scattered throughout the white and the gray matter of the frontal lobes.

REPORT OF CASES

CASE 1.—A white man aged 28 was admitted to the Cincinnati General Hospital immediately after an accident in which his car was demolished by a train. The patient was in deep coma on admission. The blood pressure was 110 systolic and 90 diastolic; the pulse rate was 150 and the respiratory rate 50 a minute. He was in acute pulmonary distress. Examination of the chest revealed that the breath sounds were almost absent on the right side and loud and clear on the left side. There was subcutaneous emphysema, extending from the level of the lower eyelids down to the inguinal ligament. The patient died five hours after the accident.

General Autopsy Observations.—The following gross abnormalities were observed post mortem: multiple fractures of the ribs bilaterally; bilateral massive

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1. Scheinker, I. M.: (*a*) Cerebral Swelling and Edema Associated with Cerebral Tumor, Arch. Neurol. & Psychiat. **45**:117 (Jan.) 1941; (*b*) Zur Histopathologie des Hirnödems und der Hirnschwellung bei Tumoren des Gehirnes, Deutsche Ztschr. f. Nervenh. **147**:139, 1938; (*c*) Ueber das gleichzeitige Vorkommen von Hirnschwellung und Hirnödem bei einem Falle einer Hypernephrommetastase des Kleinhirns, ibid. **148**:1, 1939.

2. Evans, J. P., and Scheinker, I. M.: Histologic Studies of the Brain Following Head Trauma: I. Post-Traumatic Cerebral Edema, to be published; II. Post-Traumatic Petechial and Massive Intracerebral Hemorrhage, to be published; III. Post-Traumatic Infarction of Cerebral Arteries, with a Consideration of the Associated Clinical Picture, Arch. Neurol. & Psychiat. **50**:258 (Sept.) 1943.

hemothorax; mediastinal and subcutaneous emphysema and mediastinal hemorrhage, and multiple hemorrhages and acute passive congestion of the lungs. The scalp was intact. Examination of the head and face revealed no evidence of laceration or ecchymosis.

Gross Examination of the Brain.—The dural cap was normal. The brain as viewed from the upper and lower surfaces showed no pathologic alterations except for considerable congestion and dilatation of the pial vessels. Throughout the coronal sections of the brain small multiple petechial hemorrhages, of variable size, were observed. They were scattered throughout the white and the gray matter indiscriminately, though they were more prominent in the white matter (fig. 1).

Microscopic Study of the Brain.—Sections from several cortical areas were stained with hematoxylin and eosin and cresyl violet and by the Loyez method for myelin sheaths, the Bodian strong protein silver method and the scarlet red method for fat.

Histologic examination revealed two principal types of abnormalities: (1) vascular alterations and (2) changes in the nerve tissue.

1. The chief histologic alterations of the vascular system may be demonstrated by a few characteristic photomicrographs. What appeared to be small punctate hemorrhages to the naked eye were recognized as small perivascular hemorrhages under low power magnification. These areas presented tremendously distended small veins or capillaries surrounded by a large ring of extravasated blood. Most of the smaller blood vessels, especially the veins and capillaries in the white substance, were congested and disclosed signs of stasis (fig. 2). Some of the engorged capillaries presented degenerative alterations of their endothelium. The walls of the distended veins were undergoing disorganization and showed an increase of permeability for serous fluid and red blood cells (fig. 3). The perivascular spaces were maximally distended and filled with extravasated serous fluid or red blood cells. The pial-glial membrane appeared disrupted and was frequently separated from the adjacent nerve tissue by a small amount of serous fluid, containing a few histiocytes or macrophages (fig. 4).

2. The following changes, secondary I believe to the circulatory disturbance, were observed in the nerve tissue proper: (*a*) About some of the congested veins were narrow streaks of loss of myelin (fig. 5). Further analysis of these perivascular lesions revealed circumscribed areas of focal necrosis, characterized by rarefaction of the tissue, cellular destruction and loss of nerve fibrils (fig. 4). These areas of degeneration contained no, or few, cellular elements. No fat granule cells were present, and no inflammatory reaction was apparent. (*b*) In some perivascular areas there were rarefaction and an alveolar, sievelike appearance of the adjacent nerve tissue, with the formation of numerous large vacuoles, separated from one another by thin trabeculae. (*c*) There were scattered small, circular hemorrhagic areas, surrounded by small areas of tissue necrosis and rarefaction.

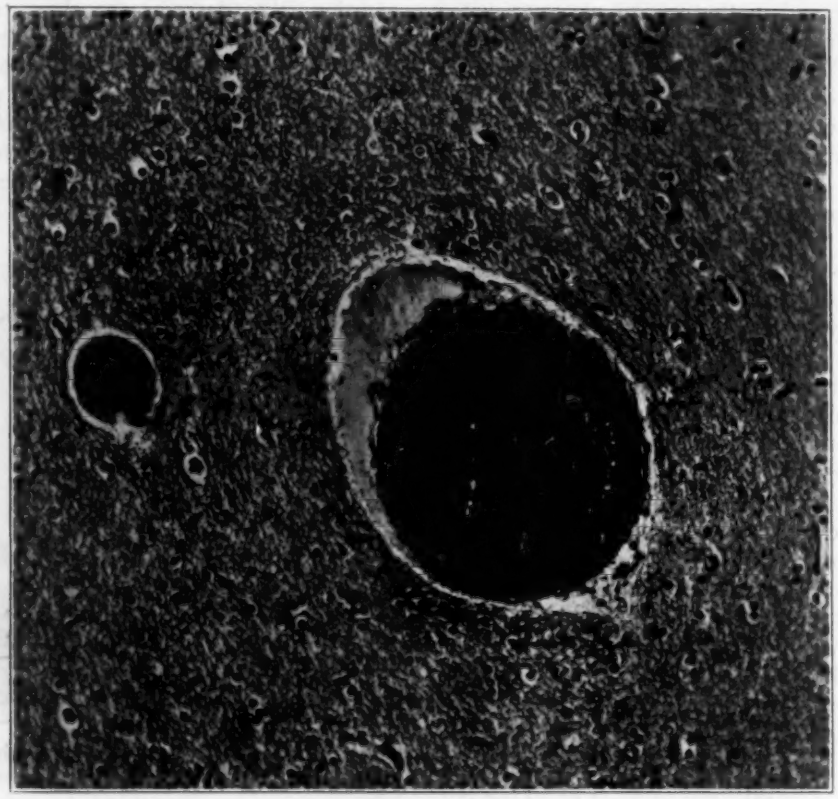

Fig. 2 (case 1).—Tremendous dilatation and stasis of the smaller veins and capillaries. Note the increased permeability of the vessel wall for serous fluid. Hematoxylin-eosin stain; × 165.

A white man aged 28 was admitted in deep coma immediately after a collision with a train. He died five hours after the injury, never having

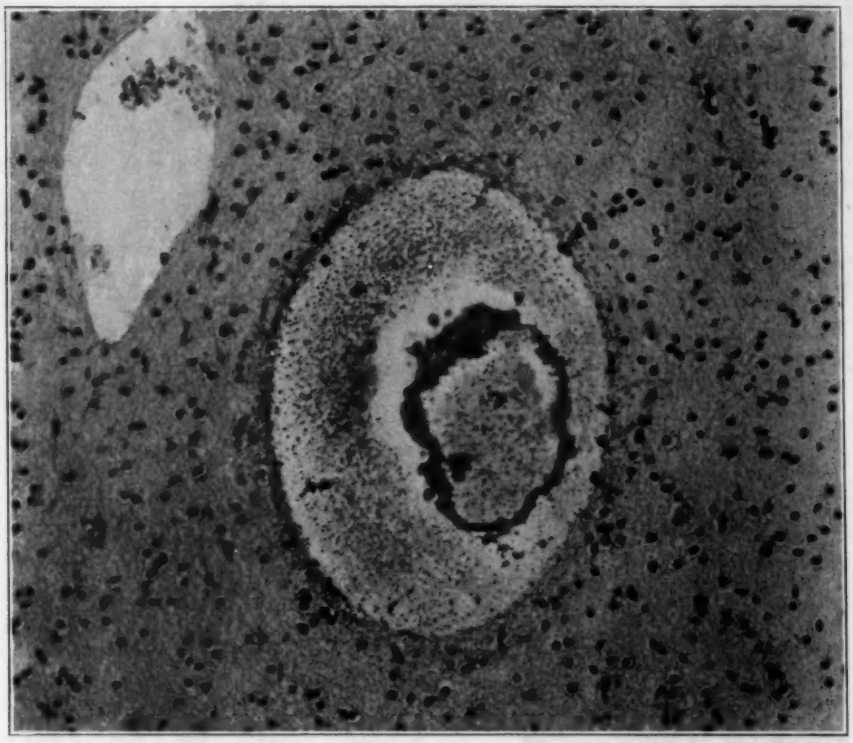

Fig. 3 (case 1).—Distended vein, with a tremendously dilated perivascular space, filled with a large number of red blood cells. Note the degenerative alterations and the disorganization of the vessel wall, associated with an increase in permeability for red blood cells. Cresyl violet stain; × 165.

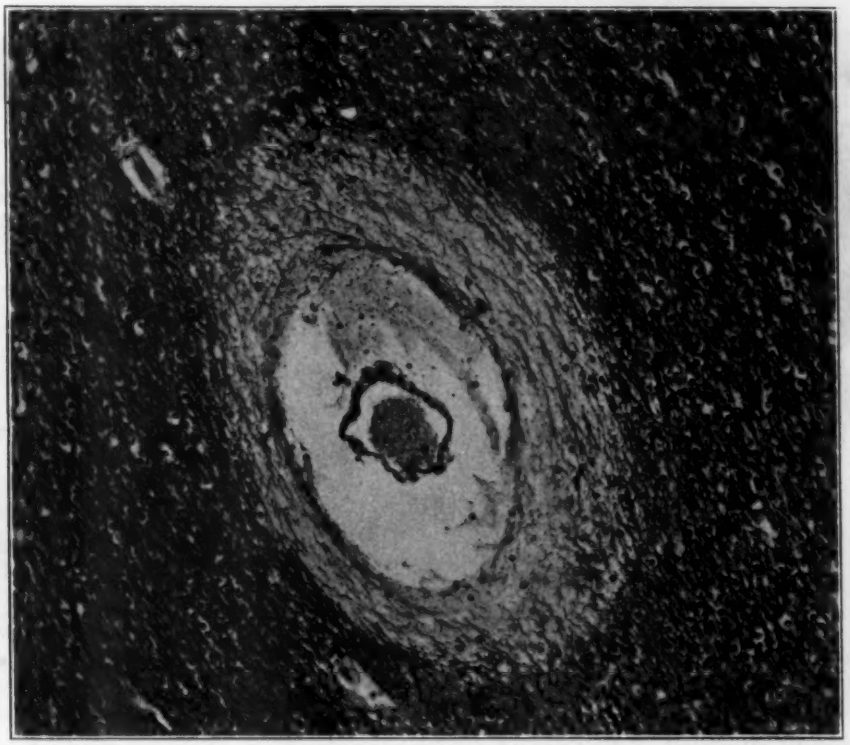

Fig. 4 (case 1).—Perivascular area of tissue destruction, with loss of nerve fibrils. The pial-glial membrane is disrupted. Bodian method of silver impregnation; × 165.

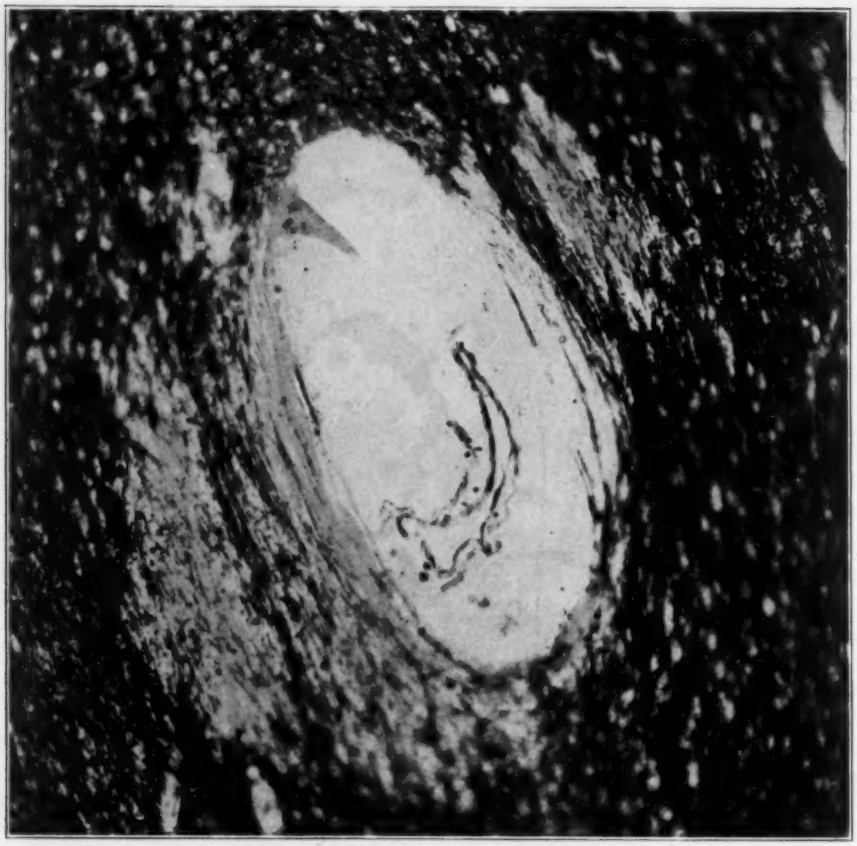

Fig. 5 (case 1).—Perivascular area of demyelination. Spielmeyer stain for myelin sheaths; × 165.

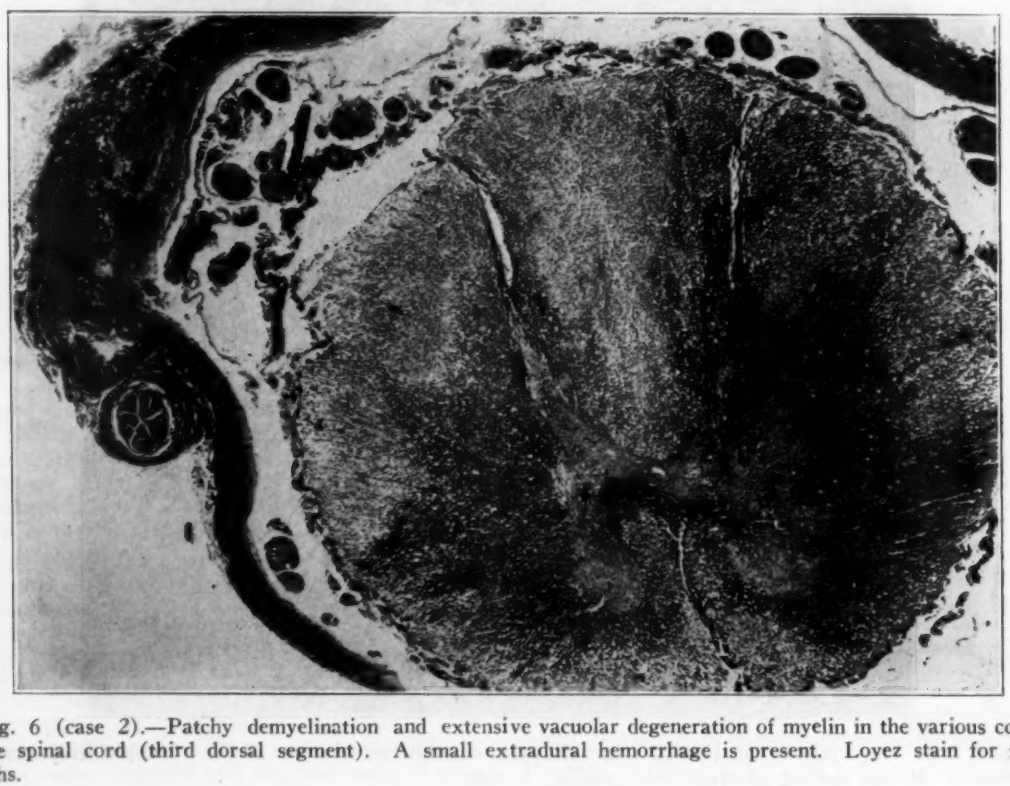

Fig. 6 (case 2).—Patchy demyelination and extensive vacuolar degeneration of myelin in the various columns of the spinal cord (third dorsal segment). A small extradural hemorrhage is present. Loyez stain for myelin sheaths.

regained consciousness. Autopsy, performed six hours post mortem, showed that the scalp was intact and that the head did not present any evidence of laceration. Coronal sections of the entire brain showed a diffuse, tremendous vascular congestion, particularly in the white matter. This congestion was associated with multiple areas of petechial and perivascular hemorrhages. Microscopic examination revealed lesions indicative of functional vascular changes, associated

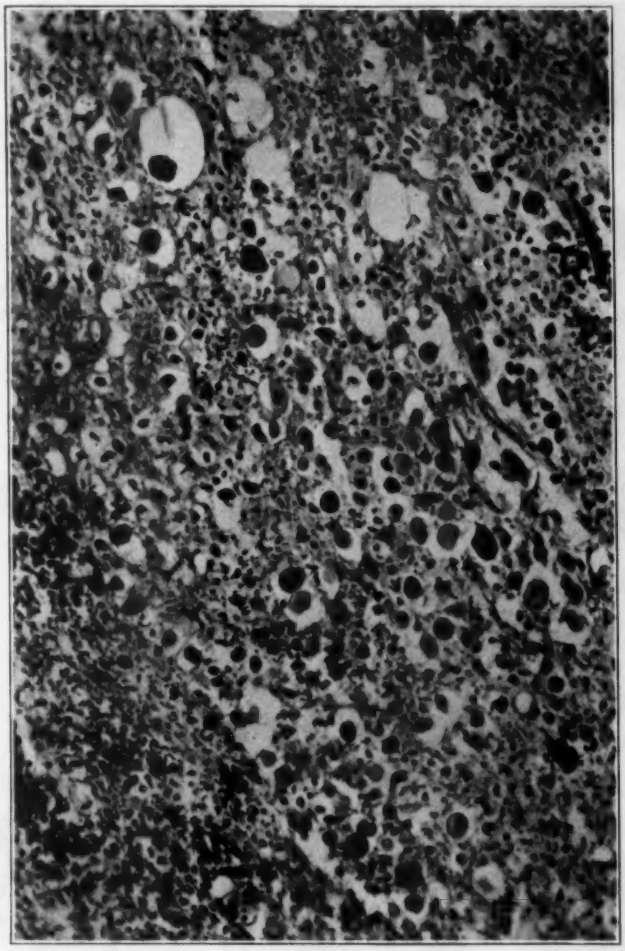

Fig. 7 (case 2).—Irregular swelling of axis-cylinders in various areas of the white matter of the spinal cord. Bodian method of silver impregnation; × 135.

with circumscribed areas of altered nerve tissue adjacent to the blood vessels.

The following case is illustrative of functional vascular disturbances associated with injury to the spinal cord.

Case 2.—A white boy aged 9 years was admitted to the Cincinnati General Hospital thirty minutes after having been shot in the neck with a .32 caliber bullet at close range. He was knocked down by the impact and immediately noted that he could not move his legs and that the lower part of his body was "numb."

Physical examination revealed that he was pale, but not in shock. His only complaint, other than that of paralysis, was fear of missing his favorite radio program if the examiner did not hurry. There was a small wound of entry just above the left sternoclavicular junction and about 2 cm. to the left of the midline. There was no wound of exit.

Neurologic examination disclosed complete flaccid paralysis of both lower extremities, with a sensory level at the second dorsal segment. The intercostal muscles were paralyzed, but the upper extremities were not involved.

The blood pressure was 140 cystolic and 80 diastolic. The respiratory rate was 22 and the pulse rate 86 per minute. Roentgenographic examination of the spine revealed a fracture of the second dorsal vertebra. Lumbar puncture disclosed a partial spinal subarachnoid block. The spinal fluid contained 1,300 red blood cells per cubic millimeter.

Course.—Within a few hours signs of atelectasis and diffuse bronchopneumonia developed. The patient died forty-eight hours after admission.

General Autopsy Observations.—The diagnosis was penetrating gunshot wound of the neck, with perforation of the left lower lobe of the thyroid, the esophagus and the second dorsal vertebral body and laceration of the outer layer of the spinal dura; diffuse bilateral bronchopneumonia and pulmonary edema.

Gross Examination of the Spinal Cord.—The upper portion of the cord and its meninges showed an area of laceration of the exterior surface of the dura, with hemorrhage. Section just below the level of injury revealed numerous punctate hemorrhages, diffusely scattered throughout the gray and the white substance, but more widespread in the gray matter. Sections from several levels of the spinal cord were stained with hematoxylin and eosin and cresyl violet; by the Spielmeyer and Loyez methods for myelin sheaths, by the Bodian 1 per cent protein silver technic and the scarlet red method.

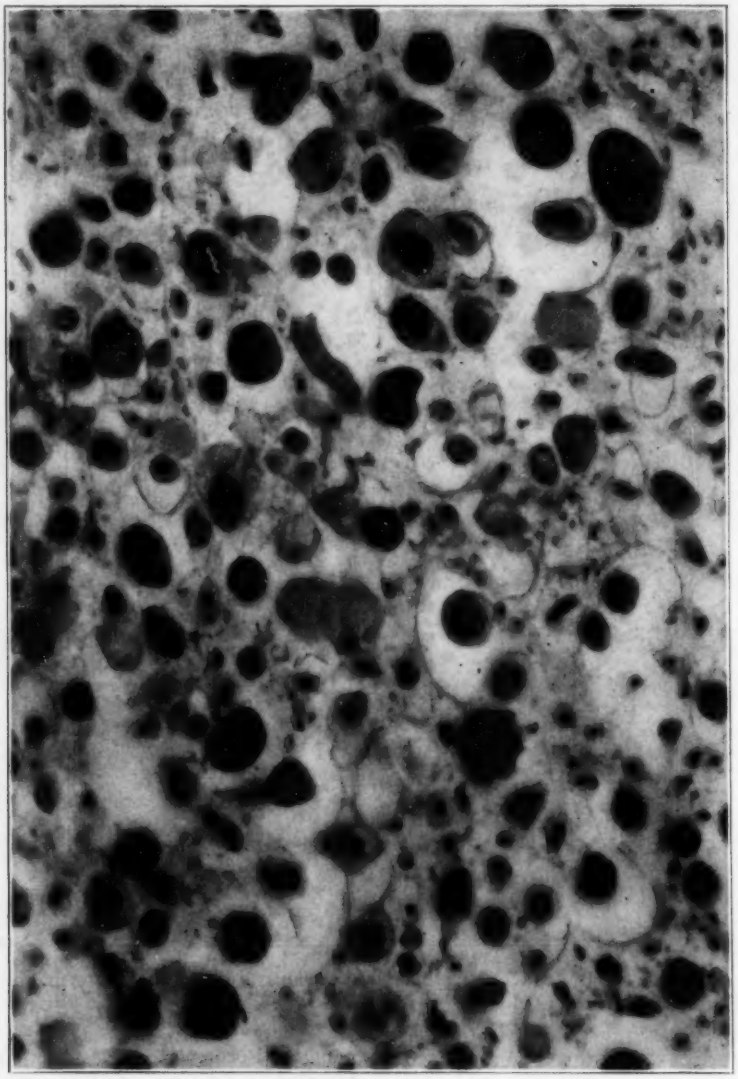

Fig. 8 (case 2).—Tremendously swollen nerve fibers of the dorsal columns of the spinal cord seen in transverse section. Note the central, more intensively stained, part, outlined by a peripheral ring of slightly impregnated substance. Bodian method of silver impregnation; × 285.

Microscopic Study of the Cord.—The most striking manifestation of the pathologic process was the presence of areas of patchy degeneration in the posterior columns and the crossed pyramidal and spinocerebellar tracts (fig. 6). The anterior pyramids were also involved. The patches of degeneration exhibited a cribriform, or areolar, appearance. The vacuoles were of various sizes and shapes and were usually empty. Some of them, especially at the periphery of the lesions, harbored tremendously thickened axis-cylinders (fig. 7). In transverse section the swollen nerve fibers appeared circular, with a central, more intensively stained, part, outlined by a ring of slightly impregnated substance (fig. 8). In the central part of the lesions, which contained more extensively deteriorated tissue, the nerve fibrils revealed more advanced lesions, in the form of fragmentation and poor impregnation.

Loyez and Spielmeyer preparations for myelin sheaths revealed extensive patchy demyelination, with extensive degeneration or complete disappearance of myelin in the various columns of the spinal cord (fig. 6). Occasionally a small number of myelin sheaths were preserved; they were irregular in outline and frequently were broken up into globules. These areas of demyelination closely resembled those described in cases of subacute combined degeneration. They were formed by vacuolation and lacunar degeneration of the tissue. The white columns appeared spongy as the result of

formation of a large number of vacuoles where the nerve fibrils and the myelin sheaths had been destroyed. These alterations were especially prominent throughout the upper thoracic region. The lower cervical region showed much better preservation. Myelin preparations revealed loss of sheaths in these areas, the disappearance of the myelin being confined to the ventral part of the dorsal column (fig. 9). This loss was associated with the formation of large vacuoles, which harbored tremendously swollen nerve fibrils.

Definite pathologic alterations were noted in some of the anterior and posterior spinal roots; these were of two types: (1) conspicuous degeneration of the nerve fibrils and (2) disintegration of the myelin sheaths. Sections stained by the Bodian protein silver method disclosed an irregular, beadlike swelling of the axis-cylinders (fig. 10). Some of the swollen fibers were in a state of disintegration, breaking up into granular debris.

Loyez preparations revealed extensive degeneration, or almost complete disappearance, of the myelin sheaths in some areas of the spinal roots (fig. 11). Some of the sheaths were irregular in outline and caliber or were broken up into globules.

The gray matter of the anterior and posterior horns disclosed no gross changes except for slight degeneration of the nerve cells and the presence of small areas of petechial hemorrhage. Some of the nerve cells of the anterior horn appeared greatly swollen (fig. 12); the nucleus was displaced to the periphery, and the stainable Nissl substance was broken up.

It should be emphasized that the spinal cord escaped a direct laceration or major injury. Only the outer surface showed the presence of an extradural clot (fig. 6). The dura was not torn. There was no massive subarachnoid bleeding; in some areas of the subarachnoid space there was a moderate accumulation of extravasated red blood cells. No other abnormalities were observed in the leptomeninges.

The medulla, pons, midbrain and cortex did not disclose any gross alterations.

The changes in the blood vessels of the spinal cord and their relation to the pathologic lesions of the nerve tissue deserve special attention. What appeared to be small punctate hemorrhages to the naked eye were recognized as small perivascular extravasations of blood under low power magnification. The center of these hemorrhages usually contained a capillary or a small vein which was plugged with blood and dilated (fig. 13). The majority of the maximally distended veins and capillaries presented all the signs of stasis and prestasis. In addition, there were beginning necrosis of the vessel wall and signs of increased permeability for serous fluid and red blood cells (fig. 14). The perivascular spaces were distended and filled with extravasated erythrocytes and serous fluid.

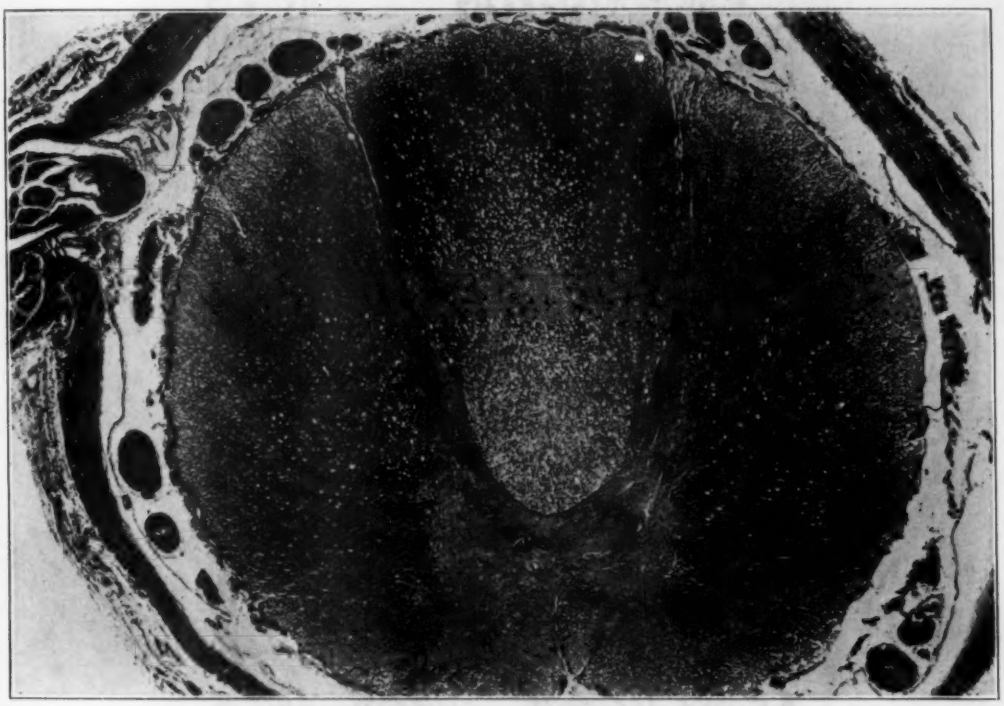

Fig. 9 (case 2).—Loss of myelin sheaths, confined to the ventral portion of the dorsal columns (fifth cervical segment). Loyez stain for myelin sheaths.

A white boy aged 9 years was admitted to the hospital thirty minutes after having been shot in the neck with a .32 caliber bullet. He immediately noted that he could not move his legs and that the lower part of his body was "numb." Physical examination disclosed complete flaccid paralysis of both lower extremities, with a sensory level at the second dorsal segment. He died forty-eight hours after the injury. Autopsy, performed four hours post mortem, showed a superficial laceration of the outer surface of the dura. The spinal cord itself was grossly without alterations except for numerous petechial hemor-

rhages, diffusely scattered throughout the gray and the white substance.

The microscopic examination revealed two types of abnormalities: (1) vascular lesions with the typical picture of vasoparalysis and stasis and (2) profound alterations of the nerve tissue proper, secondary to the circulatory disturbances, in the form of extensive patchy demyelination, vacuolation and lacunar degeneration of the white columns. This was associated with degenerative alterations of the anterior and posterior spinal roots.

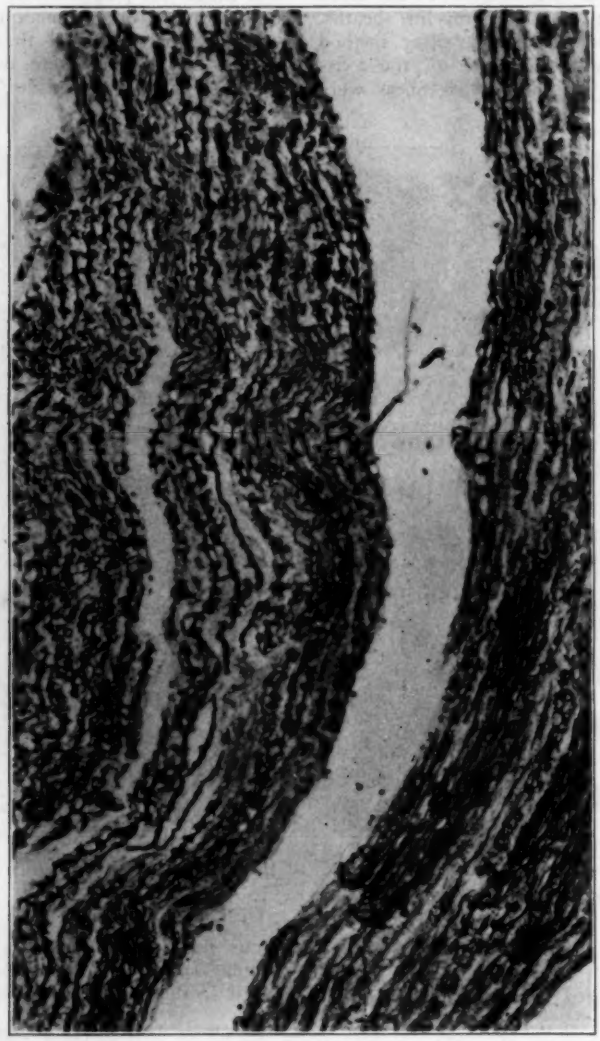

Fig. 10 (case 2).—Irregular, beadlike swelling of the nerve fibrils in one of the posterior spinal roots. Bodian method of silver impregnation; × 135.

THEORETIC CONSIDERATIONS

Definition of the Syndrome Vasoparalysis.—The cases reported here have in common an alteration of the blood supply of the central nervous system as the result of a definite type of vascular disturbance, best characterized as vasoparalysis of the central nervous system, or "central vasoparalysis."

The morphologic features of the syndrome may be described as follows: (1) maximal distention and engorgement with blood of the smaller veins and capillaries, associated with signs of stasis; (2) degenerative changes or complete necrosis of the vessel wall, with an increase in permeability for serous fluid and red blood cells, and (3) distention of the perivascular spaces, which usually harbored extravasated fluid and red blood cells.

Occurrence.—All these changes may be observed as a result of any acute physical or chemical irritant. Of the former, trauma should be especially emphasized. Chemical irritants may include poisons of every kind. I recently had

the opportunity to study the histopathologic changes in the brain in 5 cases of arsphenamine encephalopathy, with vascular alterations typical of vasoparalysis. A detailed description of the observations in these cases is given elsewhere.[3]

On the basis of my studies, I consider vasoparalysis as a frequent reaction of the blood vessels of the nervous system, due to acute damage in the form of trauma or intoxication.

Ricker[5] and Nedzel.[6] Ricker's fundamental work demonstrated that profound circulatory disturbances may result from traumatic stimuli applied to the vessel wall and may be propagated along the vessel. Stimulation of the vessel wall by weak trauma usually results in a brief contraction of the vessel, after which the exposed vessel soon dilates. This paralytic dilation is usually accompanied by what appears to be a

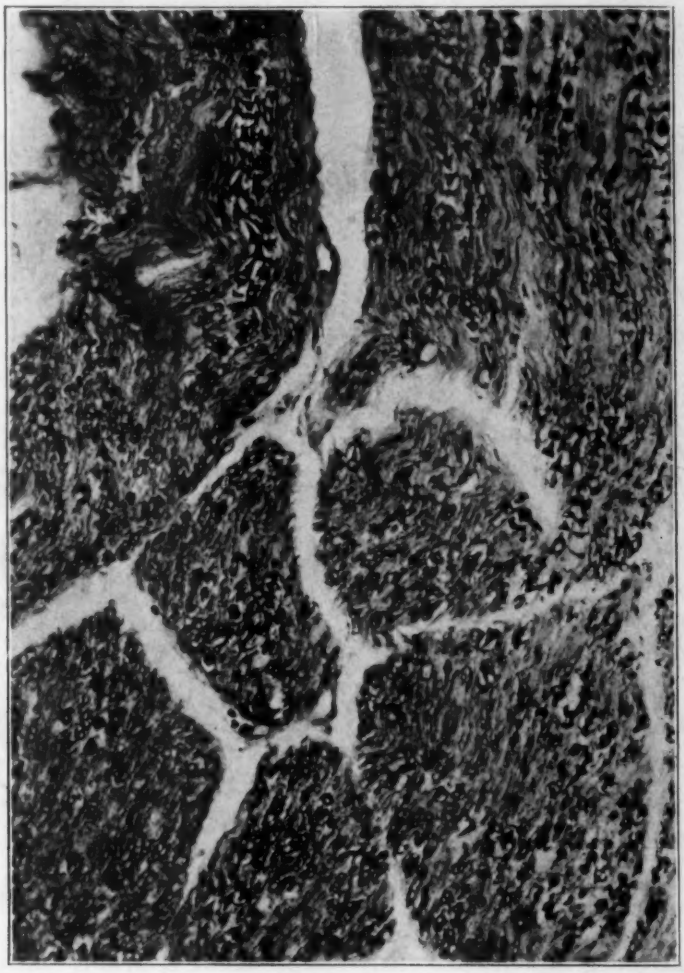

Fig. 11 (case 2).—Extensive degeneration of the myelin sheaths in one of the posterior spinal roots. Loyez stain for myelin sheaths; × 135.

Experimental Evidence of the Occurrence of Vasoparalysis as the Result of Physical and Chemical Irritants.—Understanding of functional vascular alterations is based particularly on the experimental researches of Cohnheim,[4] slowing down of the blood stream. This showing gradually becomes more pronounced, and if the irritant is sufficiently intense, there may be complete stasis or stoppage of the local circu-

3. Scheinker, I. M.: Genesis of Encephalopathy Due to Arsphenamine (Central Vasoparalysis Due to Arsphenamine), Arch. Path. **37**:91 (Feb.) 1944.

4. Cohnheim, J.: Lectures on General Pathology, translated by A. B. McKee, London, New Sydenham Society, 1889.

5. Ricker, G.: Die Entstehung der pathologisch anatomischen Befunde nach Hirnerschütterung in Abhängigkeit von Gefössnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919.

6. Nedzel, A. J.: Vascular Spasm: Experimental Studies, Urbana, Ill., University of Illinois Press, 1943.

lation. Villaret and Cachera,[7] studying experimental emboli of powdered glass, reported that the pial arterioles showed abnormal irritability weeks after embolism was produced. Forbes [8] stated that "trauma to vessel walls causes the greatest change in tonus" and observed that under experimental conditions "true spasm" of pial arteries is seen after strong mechanical or electrical stimuli applied directly to the vessels.

Putnam,[9] in his experimental studies, showed that stimulation of cervical sympathetic fibers causes an average reduction in blood flow of approximately 15 per cent, the systemic arterial blood pressure remaining constant.

tions examined the changes in the nerve tissue. It is of interest that on many occasions Nedzel observed definite dilatation and congestion of the smaller vessels, with the "typical picture of white stasis." These "definite vascular alterations" were associated with the following degenerative lesions of the perivascular nerve tissue: edema and swelling of the myelin sheaths and axons, hydration, necrobiosis and neuronophagia of the nerve cells. The vascular alterations in the spinal cords of the dogs which were given injections of pitressin and were killed one and a half hours after receiving a single injection were similar to those described as vasoparalysis. It

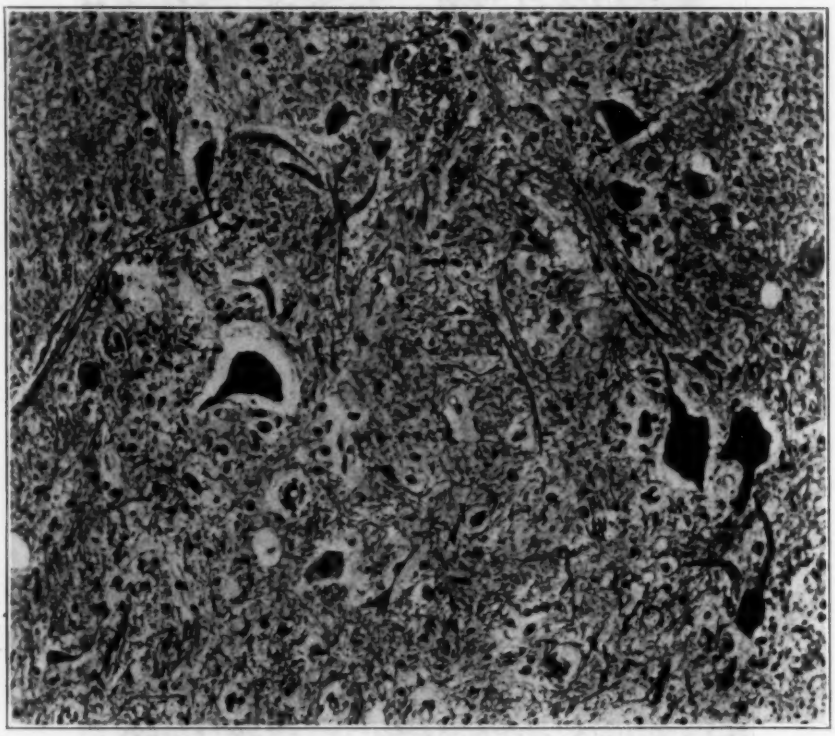

Fig. 12 (case 2).—Degenerative alterations of the nerve cells of the anterior horn (third lumbar segment). Bodian method for silver impregnation; × 165.

Nedzel,[6] in his interesting experimental study of vascular spasm, contributed to a better understanding of the underlying morphologic features associated with functional vascular disturbances. He approached the problem of vascular spasm from the morphologic and the physiologic side. He made use of single or repeated injections of pitressin and at varying periods after such injec-

is presumed, therefore, that some of the vascular alterations observed by Nedzel could be regarded as a reactive vasoparalysis following a vascular spasm of short duration. On several occasions Nedzel described vasodilatation, congestion, white stasis and extravasation of red blood cells into the perivascular spaces—changes typical of vasoparalysis. It should be emphasized that, since a vascular spasm seldom lasts more than a few seconds, it is doubtful whether its morphologic equivalent could be observed.

PHYSIOLOGIC CONSIDERATIONS

It should be emphasized that vascular dilation in itself could not be considered as absolute evi-

7. Villaret, M., and Cachera, R.: Les embolies cérébrales, Paris, Masson & Cie, 1939.

8. Forbes, H. S.: Physiologic Regulation of the Cerebral Circulation, Arch. Neurol. & Psychiat. **43**: 804 (April) 1940.

9. Putnam, T. J., cited by Cobb, S.: The Cerebral Circulation: XXV. Remarks on Clinical Physiology, Ann. Int. Med. **7**:292, 1933.

dence of vascular disturbance. A certain degree of congestion may be physiologic. Passive hyperemia is frequently observed in agonal states. A certain degree of dilation may accompany an accelerated, or at any rate not a diminished, blood flow (Ferris [10] and others). Mere dilation of an otherwise normal blood vessel in itself need not indicate slowing of the blood flow. In cases, however, in which a tremendous dilation of the blood vessels is associated with definite structural changes of the vessel wall, resulting in increased permeability for serous fluid and red blood cells—changes typical of vasoparalysis of the central nervous system—there is more evidence for a detrimental vascular disturbance. Ricker [5] and Tannenberg,[11] in their experimental observations, expressed the opinion that the

Fig. 13 (case 2).—Stasis of the vessels of the spinal cord (seventh dorsal segment). Note the degenerative alterations of the vessel wall and the tremendously distended perivascular spaces, filled with large masses of extravasated blood. Hematoxylin-eosin stain; × 135.

10. Ferris, E. B.: The Effect of High Intracranial Venous Pressure upon the Cerebral Circulation and Its Relation to Cerebral Symptoms, J. Clin. Investigation **18**:19, 1939.

11. Tannenberg, J.: Experimentelle Untersuchungen über lokale Kreislaufstörungen, Frankfurt. Ztschr. f. Path. **31**:173, 182, 285, 351 and 385, 1925.

combination of dilatation and diapedesis constitutes typical signs of slowing of the blood stream. Similar views have been expressed by Campbell, Alexander and Putnam,[12] who stated the opinion that this combination is indicative of "a vascular disturbance likely to be detrimental to the parenchyma." The term stasis, from a physiologic point of view, designates a cessation of blood flow associated with a change in the ratio of blood corpuscles to plasma. The most important factor is apparently the concentration of the red blood cells. Krogh and Harrog,[13] in their interesting experiments dealing with capillary permeability, produced stasis, dilation and increase in the permeability of the capillary wall by use of solutions of ethyl carbamate. They observed microscopically a concentration of the corpuscles, produced by the rapid loss of plasma through a capillary wall the permeability of which had been greatly increased. The viscosity of the concentrated blood caused the flow first to become sluggish and finally to cease entirely, as the venous capillaries became completely filled with solid cylinders of tightly packed blood cor-

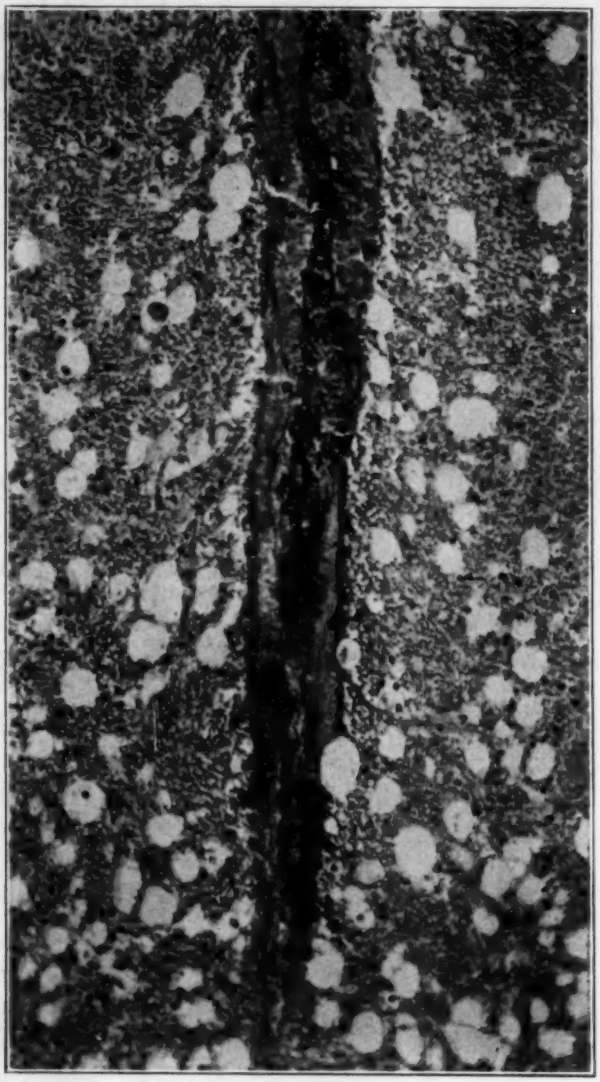

Fig. 14. (case 2).—Longitudinal section through a vein of the spinal cord (fifth dorsal segment). Note the degenerative changes and disorganization of the vessel wall associated with an increased permeability for serous fluid and red blood cells. The perivascular space is distended and filled with extravasated blood. The surrounding tissue shows an early stage of vacuolar degeneration. Hematoxylin-eosin stain; × 135.

12. Campbell, A. C. P.; Alexander, L., and Putnam, T. J.: Vascular Pattern in Various Lesions of the Human Central Nervous System, Arch. Neurol. & Psychiat. **39**:1150 (June) 1938.

13. Krogh, A., and Harrog: J. Physiol. **54**:125, 1921.

puscles. Krogh and Harrog [13] concluded that the increased permeability observed after the application of ethyl carbamate to the peripheral circulation is due merely to the capillary dilation. Landis [14] was able to show that the primary cause of the stasis produced by ethyl carbamate is the toxic injury of the endothelium of the capillary wall by the drug, accompanied by a high capillary pressure. The experiments described by Landis are pertinent. Dye solutions were injected through a micropipet inserted into the lumen of the capillary. It was observed that the dye at once passed through the portion of capillary wall that had been subjected to trauma. It required several minutes, however, for the dye to appear outside the normal endothelium. "It was concluded, after ruling out the possibility of leakage, that mechanical pressure increased the permeability of the capillary wall by an injury effect." According to Landis, mechanical compression of venous capillaries may produce the typical picture of stasis, which he described as follows:

> The central cells are slowly pushed forward by the pressure of the arterial side. Finally they are forced completely through, and circulation is resumed through a hollow cylinder of erythrocytes, which are closely adherent to the damaged endothelium. This stickiness of the injured wall is very characteristically seen after the capillary is injured either chemically or mechanically.

In addition, the same picture of stasis has been produced by a series of substances (acids, alkalis, ether, chloroform and alcohol). In each case the first notable change was the tendency of the erythrocytes to stick fast to the endothelium, which was shortly followed by the development of typical stasis.

PATHOPHYSIOLOGIC MECHANISM OF VASOPARALYSIS

From the experimental background and the clinical pathophysiologic observations, one may proceed to a consideration of the mechanism of the vascular changes described as vasoparalysis. The histologic changes described in and about the smaller blood vessels in the aforedescribed cases provide an important clue to the mechanism. The changes in the nerve parenchyma in each case were considered secondary to local circulatory disturbances. In neither case was there evidence of direct traumatic alteration of the nerve parenchyma. In the first case there was no fracture of the skull and no laceration of the surface of the brain; in the case of injury of the spinal cord there was, except for a slight contusion of the outer surface of the dura, no major injury of the spinal cord itself. These observations suggest the following theory of the mechanism: As the result of trauma, vasoparalysis occurs in some unknown manner, and the smaller veins and capillaries dilate to such an extent that actual slowing of the blood stream and partial or complete stasis result. The vascular dilation, which is so striking a feature, may be due to paralysis of the muscular fibers of the small blood vessels. According to Krogh and Harrog, even the capillaries possess contractile power and may be paralyzed. The question regarding the role of the nervous mechanism of the affected vessel must be left to the physiologist. It may be presumed that the chief action is an indirect one, probably transmitted over the neurovascular network to the distant subdivisions of the vascular tree, since profound circulatory disturbances may be seen in regions remote from the direct influence of the irritant stimulus.

The slowed circulation leads to the local accumulation of carbon dioxide and other metabolites. Carbon dioxide is a particularly active vasodilator. Its accumulation results in further vascular dilation and increased permeability of the vessel wall. If these alterations are sufficiently severe, actual degeneration and necrosis of the vessel walls may occur.

In some of my cases I observed profound structural alterations of the small vessels, particularly the veins and capillaries. The sharpness of outline of the individual tissue elements which constitute the vessel wall may be lost; the wall becomes looser in texture, and its outer limit is nebulous. The endothelial cells of the capillaries do not remain passive. The lining cells first become enlarged and proliferate; in later stages they are for the most part completely degenerated.

The most essential vascular factor is the increased permeability of the vessel wall. The most permeable section of the small vessels appears to be at the point of transition between capillaries and venules. It is at this point that oxygen tension is at its lowest, and the resistance of capillary endothelium to permeation depends on an adequate supply of well oxygenated blood. The retarded circulation no doubt interferes with the adequate supply of oxygenated blood to the capillaries. Their walls become more permeable. The solid and the fluid constituent of the blood penetrate the vessel walls. The resulting accumulation of large masses of serous fluid and red blood cells in the tremendously distended perivascular spaces serves, in turn, further to retard circulation and contribute to the hypoxia of the

14. Landis, E. M.: Micro-Injection Studies of Capillary Permeability, Am. J. Physiol **81**: 124, 1927.

nerve tissue. There seems no doubt that these physiologic changes interfere with proper exchange of oxygen and carbon dioxide, so that the normal tissue metabolism becomes increasingly disturbed and incompatible with the maintenance of normal function.

SUMMARY

Recent studies have indicated that vascular disturbances are of great significance in the production of cerebral edema and tissue alterations seen in numerous cases of injury to the brain.

The characteristic morphologic features of a special type of vascular disturbance and the associated histopathologic changes suggest that the syndrome can best be characterized as vasoparalysis of the central nervous system, or "central vasoparalysis."

In 2 illustrative cases of injury to the brain or the spinal cord autopsy did not disclose gross destruction of the tissue of the brain or the spinal cord.

In both cases histologic examination disclosed diffuse vascular disturbances which presumably would account for the alterations seen in the nerve tissue proper.

Cincinnati General Hospital.

SYNTHESIS OF HIPPURIC ACID IN DEMENTIA PRECOX

STANLEY T. MICHAEL, M.D.
HARTFORD, CONN.
MAJOR JOSEPH M. LOONEY, M.D.
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
EMBRIE J. BORKOVIC, M.D.
WORCESTER, MASS.

The numerous reports of physiologic derangements associated with schizophrenia include claims of a decreased ability of the patient to synthesize hippuric acid from ingested sodium benzoate. The low rate of synthesis was first pointed out by Quastel and Wales,[1] who emphasized its frequent occurrence in catatonic patients. Its validity, subsequently denied by Ström-Olsen, Greville and Lennon,[2] the observation was again confirmed by Finkelman, Hora, Sherman and Horwitt.[3]

The synthesis of hippuric acid ($C_6H_5.CONH.CH_2.COOH$) from benzoic acid ($C_6H_5.COOH$) and aminoacetic acid ($NH_2.CH_2.COOH$) is said to be performed principally by the liver and to a small extent by the kidney. It is considered a mechanism of detoxication and is frequently used for clinical estimation of hepatic damage. The synthesis and excretion of hippuric acid in man has been reviewed by Quick.[4]

In view of the theories which assume a toxigenic origin of mental disorders, it was considered desirable to elucidate the nature of the suspected inefficiency of the liver in detoxifying benzoic acid, and the problem was approached by a detailed study of the rate of synthesis of hippuric acid in samples of urine collected at hourly intervals and by a correlation of the rate of synthesis with changes in excretion of uric acid and in the levels of lactic and pyruvic acids in the blood.

The synthesis of hippuric acid is accompanied by a retention of uric acid[5] which is proportional to the amount of sodium benzoate present in the organism at the time of the uric acid retention.[6] The determinations of lactic and pyruvic acid in the blood were included on the basis of the observations of Gibson and Doisy,[7] who reported a decrease in excretion of uric acid following the ingestion of lactic acid ($CH_3.CHOH.COOH$) and an increase following the ingestion of its oxidation product, pyruvic acid ($CH_3CO.COOH$). These studies were expected to give a possible clue to the intermediate mechanism of the synthesis of hippuric acid.

METHODS

The subjects of the study were 30 male schizophrenic patients with no evidence of physical disease and a group of 9 male control subjects, consisting of medical students, nurses and attendants. Owing to difficulties in obtaining reliable samples of urine only 19 relatively complete studies were obtained from a group of 18 schizophrenic subjects. The average age of the patients was 32; the average height, 171 cm.; and the average weight, 60.2 Kg. The 9 control subjects had an average age of 25 years, an average height of 172 cm. and an average weight of 66.4 Kg. Several statistical analyses derived from samples of blood alone were applied to larger numbers of patients. The number of subjects is given with each analysis.

All subjects were studied in a fasting state and were lying in bed during the period of the study. The experimental conditions were arranged on a pattern similar to that of the hepatic function test devised by Quick:[8] The subjects voided at approximately 7 a. m. A sample of urine was collected at approximately 8 a. m. and was followed immediately (within one minute) by the

From the Memorial Foundation for Neuro-Endocrine Research, and the Research Service of the Worcester State Hospital.

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7. Gibson, H. V., and Doisy, E. A.: A Note on the Effect of Some Organic Acids upon the Uric Acid Excretion of Man, J. Biol. Chem. **55**: 605, 1923.
8. Quick, A. J.: The Synthesis of Hippuric Acid: A New Test of Liver Function, Am. J. M. Sc. **185**:630, 1933.

administration of 80 mg. of sodium benzoate per kilogram of body weight, diluted in approximately 30 cc. of water. One drop of oil of peppermint was added to each dose as a corrigent of flavor. Four samples of urine were collected at hourly intervals after the ingestion of the benzoate. Samples of blood from a cubital vein were obtained, with a minimum amount of stasis, on approximately the half-hour of the pretest period and of the second and fourth periods following ingestion of the sodium benzoate. All intervals were timed to the nearest minute of actual collection of the sample. One glass of water was given five to ten minutes before each voiding to facilitate formation of urine.

One half-volume of each sample of urine was used for the gravimetric determination of hippuric acid by Weichselbaum and Probstein's [9] modification of the method of Quick,[8] with sodium chloride saturation. Medium grade fritted glass filters were used for collection of precipitates. The uric acid in the urine and the blood serum was determined with the photoelectric colorimeter according to the method of Folin.[10] A portion of the sample of blood was stabilized with iodoacetate and oxalate, chilled and within three minutes precipitated with trichloroacetic acid. Pyruvic acid in the filtrate was estimated as its dinitrophenylhydrazone according to the directions of Bueding and Wortis; [11] lactic acid in the same filtrate was determined by the method of Barker and Summerson.[12]

RESULTS

There was no difference between the schizophrenic and the control group in the average amount of sodium benzoate detoxicated in four hours. The average amount of sodium benzoate per kilogram of body weight synthesized to hippuric acid by the group of patients was 59.8 mg. (19 determinations), while that synthesized by the control group was 60 mg. (9 determinations). Thus, both groups detoxicated approximately 75 per cent of the ingested 80 mg. of sodium benzoate per kilogram of body weight. However, the two groups differed from each other in the range of amounts of hippuric acid synthesized. While the amount of sodium benzoate detoxicated in four hours by the control subjects was within the range of 53 to 67 mg. per kilogram of body weight, the range for 3 of the patients fell below these values, and 3 patients exceeded the performance of the best control subject.

The results of the tests for the synthesis of hippuric acid are presented in the table. The patients and the controls are grouped separately and in the ascending order of the rate of synthesis during the second hour period. The rate of synthesis is expressed in milligrams of sodium

Rate of Synthesis of Hippuric Acid, Expressed as Milligrams of Sodium Benzoate per Kilogram of Body Weight Excreted as Hippuric Acid in a Group of Schizophrenic Patients and of Normal Control Subjects, with Values for Pyruvic Acid in the Blood Before Ingestion of Benzoate and One and a Half and Three and a Half Hours Following Ingestion of Benzoate*

Subject	Age, Yr.	Weight, Kg.	Subtype of Schizophrenia	Sodium Benzoate, Mg./Kg. of Body Weight: Hour of Synthesis 1st	2d	3d	4th	Total	Pyruvic Acid, Mg./100 Cc.: Before Synthesis	Hour of Synthesis 2d	4th
T. G.	48	68	Mixed	8	8	21	18	55	0.98	1.00	1.05
F. S.	40	64	Paranoid	7	10	12	15	44	0.64	0.62	0.72
F. T.	40	58	Simple	7	12	18	20	57	0.75	0.75	0.65
H. T.	25	65	Hebephrenic	8	12	13	16	49	....	....	....
A. D.	38	54	Hebephrenic	12	12	18	17	59	0.80	0.85	0.96
R. W.	26	61	Catatonic	10	13	21	17	61	0.79	0.79	0.92
F. M.	25	55	Paranoid	11	14	15	13	53	0.75	0.92	0.96
T. F.	46	51	Paranoid	11	14	19	12	56	0.82	0.75	0.86
P. M.	21	54	Hebephrenic	14	14	19	16	63	....	....	....
A. T.	47	61	Catatonic	12	17	18	8	55	0.61	0.85	0.65
E. S.	29	58	Hebephrenic	14	18	20	12	64	0.76	0.62	0.75
R. W.	26	59	Catatonic	14	18	20	18	70	0.79	0.63	0.70
E. P.	27	64	Hebephrenic	20	19	24	10	73	0.79	0.68	0.73
B. M.	34	58	Hebephrenic	38		19	7	64	0.85	0.92	0.92
G. C.	40	68	Paranoid	10	20	22	11	63	0.75	0.80	0.73
J. C.	23	49	Hebephrenic	16	20	23	15	74	0.84	1.00	0.72
C. A.	38	76	Mixed	13	22	28		63	0.99	0.77	0.72
G. F.	25	57	Hebephrenic	14	27	24		65	1.30	1.80	1.10
C. C.	24	62	Catatonic	24	23	1		48	1.15	....	1.62
R. M.	26	84	Control	10	13	14	17	54	0.75	0.65	0.65
J. D.	24	66	Control	10	13	17	16	56	0.94	1.09	0.87
H. P.	25	75	Control	12	14	15	19	60	0.92	0.77	0.87
C. P.	28	80	Control	12	14	16	15	57	0.84	0.62	0.65
G. S.	24	75	Control	10	15	15	16	56	0.80	0.79	0.80
C. L.	25	84	Control	8	17	15	13	53	0.68	0.67	0.65
S. O.	28	89	Control	12	17	25	11	65	1.16	0.86	0.93
D. C.	24	62	Control	13	18	20	11	62	0.85	0.85	0.85
F. G.	24	58	Control	13	22	23	9	67	0.74	0.67	0.87

* The values for several of these patients have been published in another series.[6]

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12. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535, 1941.

benzoate per kilogram of body weight excreted as hippuric acid in the time designated. It may be noted from the hour to hour excretion rates that several of the patients (the first 4 subjects in the table) synthesized relatively small amounts of hippuric acid during the first two hours of the test, while 2 patients (C. C., who was in catatonic excitement during the test, and E. P.) synthesized unusually large amounts immediately during the first hour.

That retardation in synthesis in the first 4 patients was not due to retarded resorption of the sodium benzoate was evident from a signifi-

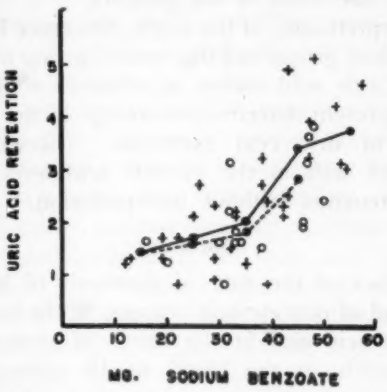


Fig. 1.—Retention of uric acid following ingestion of sodium benzoate in a group of schizophrenic patients (plus signs and solid line) and in a group of control subjects (small circles and broken line). On the ordinates are plotted the ratios of the pretest excretion rate of uric acid to excretion rates for the third and fourth hours following ingestion of sodium benzoate, and on the abscissas, the amounts of sodium benzoate, expressed in milligrams per kilogram of body weight not excreted as hippuric acid at the time corresponding to the retention of uric acid indicated on the ordinate. A detailed description of the calculations is given elsewhere.[6]

cant retention of uric acid which occurred in all these subjects during the first hour of the test. It has been shown elsewhere [6] that the retention of uric acid during the synthesis of hippuric acid is correlated with the amount of sodium benzoate absorbed in the organism. Synthesis of the absorbed benzoate to hippuric acid inactivates the uric acid retention properties of the benzoate.

Consequently, the uric acid retention may be taken as an indicator that the ingested sodium benzoate is being absorbed in excess of the amount that is concurrently synthesized to hippuric acid. Even the 2 patients who excreted large amounts of hippuric acid during the first hour of the test showed a moderate degree of uric acid retention at this time. The resorption of benzoate evidently proceeded with sufficient rapidity to supply adequate amounts of substrate for the synthesis and was not a limiting factor in the rate of synthesis in this series of subjects.

Retention of uric acid was more pronounced in the patients than in the controls after ingestion of comparable amounts of benzoate. Thus, in the patient group the excretion of uric acid decreased from a preexperimental value of 29 mg. per hour (standard error of the mean $\pm$ 2.39, for 16 subjects) to 7.7 $\pm$ 0.49 mg. per hour during the second hour following ingestion of benzoate. For the control group (8 subjects) comparable values were 29.5 $\pm$ 3.18 mg. per hour, for the preexperimental excretion, and 10.2 $\pm$ 0.63 mg. per hour, for the second hour following ingestion of benzoate. The difference between the means for the second hour is statistically significant ($t = 3.12$; $P < 0.01$).

Comparable amounts of ingested sodium benzoate caused a slightly higher retention of uric acid in the schizophrenic patients than in the controls, as shown in figure 1.

The pyruvic acid level of the blood was influenced considerably by the ingestion of sodium benzoate. The majority of subjects presented a shift from the preexperimental level of pyruvic acid one and a half hours after ingestion of

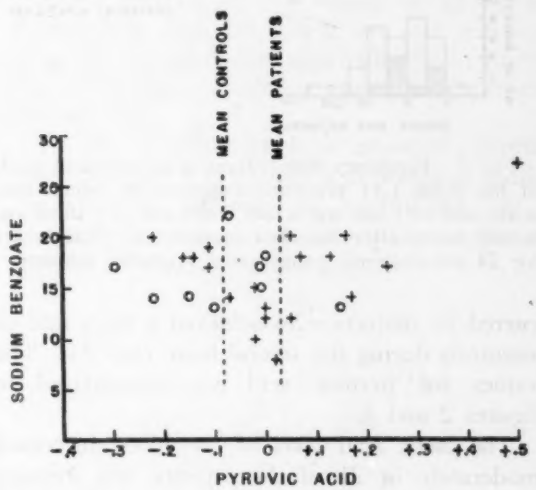


Fig. 2.—Increase or decrease in the pyruvic acid content of the blood, expressed in milligrams per hundred cubic centimeters, over the pretest level (0), one and one-half hours after ingestion of sodium benzoate (abscissas) correlated with the rate of synthesis of hippuric acid, expressed in milligrams of sodium benzoate per kilogram of body weight excreted during the second hour following ingestion of benzoate (ordinates).

benzoate. The shift was about equally distributed between an increase and a decrease in the patient group, while a decrease predominated in the control group. In about one-third the subjects the pyruvic acid was found at approximately the same level as before ingestion of benzoate.

The difference between the mean shift in the pyruvate level for the patients and that for the controls was found not to be statistically significant at the 0.01 probability level.

The shift in the pyruvic acid level seemed to be somewhat correlated with the rate of synthesis of hippuric acid. At the extreme values, the lowest rates of synthesis were accompanied by little change in the pyruvic acid level, while the greatest changes in the pyruvic acid level occurred in subjects who achieved a high rate of synthesis during the second hour (fig. 2). The values for pyruvic acid are summarized in figures 2 and 3.

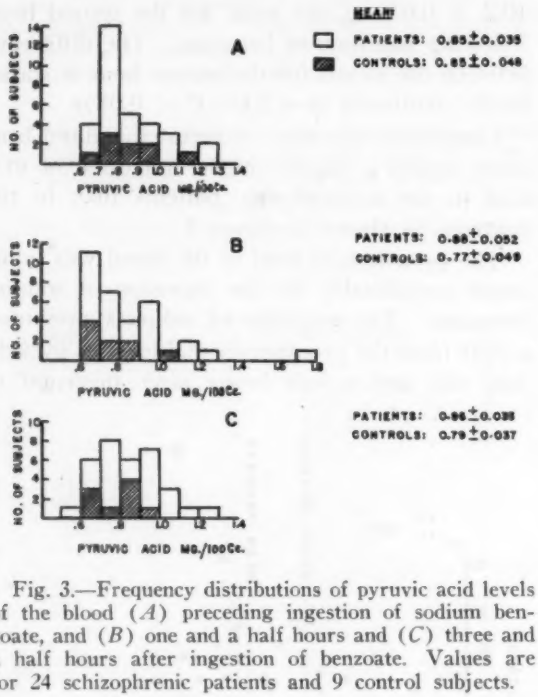


Fig. 3.—Frequency distributions of pyruvic acid levels of the blood (*A*) preceding ingestion of sodium benzoate, and (*B*) one and a half hours and (*C*) three and a half hours after ingestion of benzoate. Values are for 24 schizophrenic patients and 9 control subjects.

The lactic acid level of the blood increased moderately in 21 of 24 patients, the average increase for the entire group being 1.5 ± 0.45 milligrams per hundred cubic centimeters one and one-half hours following ingestion of benzoate. No correlation between the increase in lactic acid and the rate of synthesis of hippuric acid was found.

COMMENT

It has been shown recently that the rate of synthesis of hippuric acid is correlated with body size.[13] If no corrections for body weight had been made in the present study, there would have been a considerable difference in favor of the control group in the average amounts of hippuric acid synthesized during the test period. No corrections for body size were reported in studies by previous authors.[14]

The results of the experiments reported here indicate that the majority of schizophrenic patients, including those of the catatonic type, have adequate ability to detoxify benzoic acid. However, some irregularity in the onset of the synthesis of hippuric acid is evident in approximately one third of the patients.

Interpretations of the slight difference between the patient group and the control group in retention of uric acid cannot be offered on the basis of the present defective knowledge of the mechanisms of uric acid excretion. Likewise, the observed shift in the pyruvic acid level of the blood remains without interpretation.

SUMMARY

Studies of the rate of synthesis of hippuric acid and of concomitant changes in the excretion of uric acid and in the levels of pyruvic and lactic acids in the blood in 18 schizophrenic patients and in 9 normal control subjects revealed that the average amount of hippuric acid synthesized in four hours was approximately the same in the two groups. Three schizophrenic patients synthesized amounts considerably less than the lowest value for the normal subjects, while 3 patients exceeded the range of the normal subjects. Unlike the normal group, several of the schizophrenic patients showed initial retardation in the rate of synthesis, and 2 patients excreted unusually large amounts of hippuric acid during the first hour of synthesis.

The ingestion of sodium benzoate caused a retention of uric acid which was slightly higher in the patient group.

The synthesis of hippuric acid was accompanied by changes in the level of pyruvic acid of the blood. These changes were somewhat correlated with the intensity of the synthesis.

Dr. Michael, 200 Retreat Avenue.

Dr. Borkovic, Worcester State Hospital.

13. Scurry, M. M., and Field, H.: Correlation of the Intravenous Hippuric Acid Test of Liver Function with Body Size, Am. J. M. Sc. **206**:243, 1943.

14. Quastel and Wales.[1] Ström-Olsen and associates.[2] Finkelman and associates.[3]

ABOLITION OF BULBOCAPNINE CATALEPSY IN THE CAT BY AC-TETRAHYDRO-B-NAPHTHYLAMINE

EDWARD F. KERMAN, M.D.
SYKESVILLE, MD.

The production of a state of catalepsy in the cat by the use of bulbocapnine was first described by Peters [1] in 1904. Much has been written subsequently regarding the manifestations of this drug in the experimental animal. Interest in this reaction is based on the resemblance of the experimentally induced cataleptic state to catatonic stupor in man.

This paper is principally concerned with the methods that have been reported to abolish or alter catalepsy produced by bulbocapnine. Only a few such agents have been described. Buchman and Richter [2] showed that cocaine eliminates the experimental catatonia at once and that the animals do not return to the former stuporous state. Furthermore, if cocaine is injected before the bulbocapnine, it prevents the appearance of the catatonic syndrome.

Paterson and Richter [3] studied the effects of carbon dioxide inhalations and of scopolamine on bulbocapnine catalepsy. They reported that the effects of carbon dioxide differ, the action depending on the amount used. In lower concentrations, of from 15 to 25 per cent, it increases the effect of bulbocapnine; in higher concentrations, of from 35 to 50 per cent, it produces a transient counteracting effect, with a subsequent increase in the cataleptic symptoms. Scopolamine produces a notable prolongation of the effects of bulbocapnine.

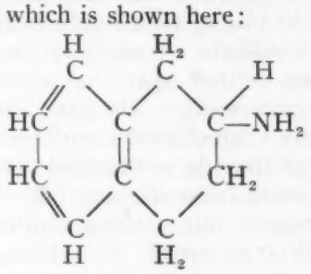
Spiegel [4] showed that amphetamine abolishes the state of catalepsy produced by bulbocapnine. He stated that if the amphetamine is injected first, the excited state that it produces is only slightly affected by a succeeding injection of bulbocapnine.

Divry and Evrard [5] investigated other drugs with respect to their ability to combat bulbocapnine catalepsy. None of the drugs they employed completely succeeded in doing this. Certain aspects of the cataleptic syndrome were lessened with use of morphine, diacetylmorphine and apomorphine hydrochloride. Caffeine produced some degree of mental alertness without altering motor inhibition. Strychnine, picrotoxin, epinephrine and scopolamine had no effect.

Kennedy [6] noted that insulin shock had no effect on the cataleptic manifestations induced by bulbocapnine. He also reported [7] that metrazol (cardiazol) greatly increased the cataleptic component of the state produced by bulbocapnine.

From analysis of the results of all of the experiments thus far noted, one can conclude that only two agents are able definitely to abolish the bulbocapnine catalepsy, namely, cocaine and amphetamine.

In the experiments here reported, another chemical agent was tested for its ability to abolish the effect of bulbocapnine in the cat. It is ac-tetrahydro-β-naphthylamine, the structural formula of which is shown here:



METHOD

Ten experiments were performed on 5 healthy cats, none of which had ever before been used for experi-

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2. Buchman, E. F., and Richter, C. P.: Abolition of Bulbocapnine Catatonia by Cocaine, Arch. Neurol. & Psychiat. **29**:499-503 (March) 1933.

3. Paterson, A. S., and Richter, C. P.: Action of Scopolamine and Carbon Dioxide on Catalepsy Produced by Bulbocapnine, Arch. Neurol. & Psychiat. **29**:231-240 (Feb.) 1933.

4. Spiegel, E.: Bulbocapnine-Benzedrine Antagonism, J. Pharmacol. & Exper. Therap. **63**:438-442 (Aug.) 1938.

5. Divry and Evrard: Recherches sur certaines substances antagonistes de la bulbocapnine, J. belge de neurol. et de psychiat. **34**:506-523 (Aug.) 1934; Psychiat. en neurol. bl. **39**:58-64 (Jan.-Feb.) 1935.

6. Kennedy, A.: Hypoglycaemic Shock and Grasp-Reflex: Effect of Insulin Shock on Bulbocapnine Catalepsy in Monkeys, J. Neurol. & Psychiat. **3**:27-36 (Jan.) 1940.

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mental purposes. Three experiments were carried out on each of 2 cats, 2 on another cat and 1 each on the remaining 2 animals. No change was made in the regular food or fluid intake of any of these animals.

Two preparations were employed: bulbocapnine ampules, containing 0.1 Gm. per cubic centimeter, and ac-tetrahydro-β-naphthylamine carbonate as a 1 per cent solution in distilled water.

Two cats were given subcutaneous injections of bulbocapnine in a dose of 25 mg. per kilogram of body weight, and the effects were noted. Three cats were given subcutaneous injections of ac-tetrahydro-β-naphthylamine in doses of 30, 5 and 1 mg. per kilogram of body weight respectively. To the last cat, after two hours, an additional dose of 2 mg. per kilogram of body weight was given. The effects were noted.

Four experiments were performed on 3 cats, all of which had been used in the previous experiments, and only after complete recovery had occurred. Characteristic catalepsy was uniformly produced by the injection of bulbocapnine in the dose of 25 mg. per kilogram of body weight. After this syndrome was definitely established, ac-tetrahydro-β-naphthylamine was given in doses ranging from 10 to 2.5 mg. per kilogram of body weight. The subsequent response was recorded.

One cat was given simultaneous injections of bulbocapnine, 25 mg. per kilogram of body weight, and ac-tetrahydro-β-naphthylamine, 2.5 mg. per kilogram of body weight. The reaction was observed.

RESULTS

Effects of Bulbocapnine Alone.—Fifteen to twenty minutes after the subcutaneous injection of bulbocapnine in the dose of 25 mg. per kilogram of body weight in 2 animals, the full cataleptic response was observed. The cats were crouched over and practically motionless. When any limb was placed in an awkward position, there was no attempt to remove it from the imposed situation. The animals could be suspended by placing their forelimbs on one chair and their hindlimbs on another. As the chairs were drawn farther apart, no attempt at self protection was made. The cats also could be placed on the edge of a table with their forelimbs hanging over the side, so balanced that the slightest move might cause them to fall. They were able to maintain this position continuously and made no effort to correct it. Although the cats frequently closed their eyes, they were not asleep, for they could open their eyes readily when they were stimulated by being touched or handled. A large barking dog was placed before 1 of the animals seventy-five minutes after injection. During the five minutes that the dog remained there, barking actively, the cat remained immobile and unperturbed. About two to two and a half hours after the injection the cats walked a few steps when urged but remained still when not disturbed. Awkward positions of the paws could still be imposed on them. Three hours after injection the same condition could still be noted. However, at this time, the chair and table tests previously mentioned gave negative results, the animal jumping to the ground but moving no further. Food was still refused at this point, the cats standing rigidly over the offered plates of milk, resisting efforts to force them to drink. Four to five hours after the intial injection complete recovery occurred.

Effects of ac-Tetrahydro-β-Naphthylamine Alone.—Experiments were performed on 3 cats, different doses of the drug being employed. It appears best to describe individually the various reactions observed.

Cat 1.—A subcutaneous injection of ac-tetrahydro-β-naphthylamine was given in the dose of 30 mg. per kilogram of body weight. Before, during and immediately after the injection the animal was docile and not alarmed over the procedure of hypodermic administration of the drug. In fifteen minutes the pupils began to dilate, and in twenty minutes they were so large that the iris was scarcely visible. About thirty minutes after injection exophthalmos appeared and lasted about twenty minutes. Several minutes after the experiment was begun the cat began to mew frequently and exhibited signs of uneasiness. Body movements became gradually more active and jerky, the animal pacing back and forth on a ledge, where it had been placed for injection of the drug. This increased motor activity was pronounced in half an hour. Ten minutes later erection of the hair on the tail could be noted. An hour after injection the animal was touched, and this caused it to jump to the floor. It lay huddled in the corner, with the fur more erect, mewing more frequently and obviously alarmed. A plate of milk was placed before it. The cat voluntarily dipped its mouth into the liquid but, before drinking, suddenly raised its eyes, too acutely apprehensive of every noise and movement in its environment to be able to consume the milk. It began to lick its fur with quick motions, never diverting its gaze from its surroundings for longer than a fraction of a second. One and a half hours after injection the cat began to pant rapidly. It was becoming more and more excited; the fur over its entire body was now erect; the pupils were widely dilated; its motions were quick and jerky, and its attention was keenly riveted on any faint sound or motion about it. At this time it was noted that the cat walked on a broader base and seemed to exhibit some degree of incoordination. Two hours after the injection the cat raised up on its hindlegs, hissed and snarled, and threw itself across the middle of the floor. It howled and attempted to right itself but could not get its legs straightened or its movements coordinated. Stimulation was now at its height. The animal continued to pant

at a furious rate and, when approached, hissed and spat. It remained in this state of helplessness for about twenty minutes. Two and a half hours after injection a slight decrease in the intensity of excitement was noted. Coordination of movements was regained. Four hours after injection the fur appeared less erect. The cat was observed continuously for nine hours. At the end of this time the pupils were still wide; the fur was only ruffled, but extreme rage was still evident, particularly when the animal was approached. Further observation could not be carried out until forty-nine hours after the drug had been given. At this time the cat had completely recovered.

CAT 2.—The animal was given ac-tetrahydro-β-naphthylamine in a dose of 5 mg. per kilogram of body weight. Before injection it was noted that the animal was a surly male, breathing fairly rapidly. However, it permitted itself to be petted and offered no resistance to the hypodermic. Eight minutes after administration of the drug drooling was noted. In ten minutes the cat suddenly appeared alarmed. The pupils dilated; panting began, with teeth chattering, and salivation was more profuse. Thirty minutes after injection the body fur was erect. Exophthalmos was observed at this time and lasted twenty minutes. From time to time, at intervals of about ten minutes, periods of apnea, of about ten seconds' duration, were noted. Except for this, panting was constant. When approached, about an hour after injection, the animal emitted a hissing snarl. Subsequent behavior was similar to that of the first cat, with one notable exception; there was at no time any evidence of incoordination. In five hours the fur was flat, but panting, mydriasis and extreme alarm were still evident. Observation was terminated here. When the cat was seen thirty-eight hours later, it had fully recovered.

CAT 3.—The animal was given the drug in the dose of 1 mg. per kilogram of body weight. The cat was noted to be a lethargic female. Within two hours after injection the only changes seen were an increase in the respiratory rate, of from 41 to 60 per minute, with no panting; moderate mydriasis, and slight ruffling of the fur. There was a moderate degree of anxiety, but the cat permitted itself to be petted. Movements were slightly increased and tended to be jerky. Two hours after injection, it being noted that no other changes were developing, an additional injection of the drug, in a dose of 2 mg. per kilogram of body weight, was given. Ten minutes later a greater degree of uneasiness was noted. The cat began to mew more frequently and the pupils to dilate more widely. Ten minutes later the cat appeared very anxious and alert; the respiratory rate was 72 a minute, and movements were more constant. The fur was more erect. Two hours later the animal's condition had reached a fairly constant level, with a great deal of alertness and apprehension but no panting, drooling or motor incoordination. There was only a moderate pilomotor response. Observation was terminated. When the cat was seen eleven hours later, it had fully recovered.

Effect of ac-Tetrahydro-β-Naphthylamine on Bulbocapnine Catalepsy. — Four experiments were performed on 3 animals. A standard dose of bulbocapnine (25 mg. per kilogram of body weight) uniformly produced the cataleptic state in fifteen to twenty minutes after injection. Once this condition was fully established, ac-tetrahydro-β-naphthylamine was given in varying doses to ascertain its effect on the stuporous state of the animal. Two cats received 10 mg.; 1 cat, 5 mg., and 1 cat, 2.5 mg. per kilogram of body weight. The cataleptic condition was completely abolished in all the animals. The following descriptions are given to present a proper picture of the reaction.

EXPERIMENT 1.—Cataleptic symptoms began to appear ten minutes after injection of bulbocapnine. At the end of one hour complete catalepsy was present, so that the cat could be suspended over two chairs without its changing its position. At this point ac-tetrahydro-β-naphthylamine, in the dose of 10 mg. per kilogram of body weight, was injected. In twenty minutes the cat began to arouse from its lethargic, motionless state and to mew frequently. Thirty minutes after the second injection the cat could no longer be placed in fixed attitudes; it mewed loudly and frequently; the pupils were slightly larger, and the respiratory rate had increased from 34 to 52 per minute. As time went on, the cat became more alert, walking about on the observation table, keenly interested in its environment and apprehensive. Four hours later the cat was still alert. It may be said that erection of fur, panting and incoordination were not observed in this experiment.

EXPERIMENT 2.—A second animal received an injection of bulbocapnine. Fifteen minutes later all the signs of catalepsy were present. Thirty minutes after injection ac-tetrahydro-β-naphthylamine, in the dose of 10 mg. per kilogram of body weight, was given. Fourteen minutes after injection of this substance the cat raised its head and began to drool profusely, and the respirations became faster. The excitement increased rapidly. Incoordination was present at this point. The cat snarled when approached. Thirty-five minutes after the second injection the

respiratory rate was 300 per minute. There was slight piloerection. Fifteen minutes after this the animal, extremely excited, was able to walk about in its cage. Twenty minutes later one could observe the same excitement and increasing mydriasis. Three hours after the second injection the animal was still panting. It snarled when approached, showing the typical effect of ac-tetrahydro-β-naphthylamine. Two hours later the action of the drug began to diminish in intensity, and in another two hours the animal had recovered completely.

EXPERIMENT 3.—Bulbocapnine was administered to a third animal. Catalepsy appeared thirteen minutes after injection. Eight minutes later ac-tetrahydro-β-naphthylamine, in a dose of 5 mg. per kilogram of body weight, was given. Thirty-five minutes after the second injection the cat was alert, inspecting its environment; its pupils were dilated. The respiratory rate was 360 per minute. Slight piloerection was noted. The animal made occasional attempts to leave its cage. Drooling was evident. Ten minutes later the cat was still more alert and unequivocally out of the cataleptic state. It was panting furiously. Movements were somewhat incoordinated. Two hours after the second injection the animal was still excited, snarling when approached and panting rapidly. The pupils were still dilated. Three hours and fifteen minutes after the second injection the cat appeared exhausted. It lay in its cage with its face buried, breathing fairly rapidly. It did not seem as alarmed as formerly, but still snarled when touched.

EXPERIMENT 4.—The same cat as that used in the preceding experiment was employed. It had completely recovered from the former experiment. Bulbocapnine catalepsy was produced in the usual manner, and ac-tetrahydro-β-naphthylamine, in a dose of 2.5 mg. per kilogram of body weight, was given six minutes after the catalepsy appeared, and nineteen minutes after the initial injection. Twenty minutes after the second drug was administered the animal was able to move slowly about the cage. It hid its head in the corners and mewed slowly and regularly. Respiration was unaltered. Thirty minutes later the cat could be seen crouched in the cage; it would not respond to the usual tests for catalepsy and had definitely recovered from the bulbocapnine state. No effects of ac-tetrahydro-β-naphthylamine were noted. One hour later the cat tried to get out of its box, where it was now being watched. It was normal in every respect and did not show the effects of either drug.

Effect of Bulbocapnine and ac-Tetrahydro-β-Naphthylamine Given Simultaneously.—One cat had injections of bulbocapnine (25 mg. per kilogram of body weight) and ac-tetrahydro-β-naphthylamine (2.5 mg. per kilogram of body weight), the two drugs being given at the same time. The animal was observed for five hours. No abnormal response was noted. It appeared that in the doses employed the drugs counteracted each other, none of the symptoms generally arising from either being observed.

COMMENT

From the foregoing report, it is apparent that ac-tetrahydro-β-naphthylamine completely abolishes the cataleptic syndrome produced in cats by bulbocapnine. Since a similar response has been obtained with amphetamine [4] and cocaine,[2] it is interesting to compare the pharmacologic activity of these drugs on the basis of their chemical structure. Ac-tetrahydro-β-naphthylamine may be considered as a sympathomimetic amine of the general type of "fatty aromatic amines without a phenolic hydroxyl group."[8] Amphetamine belongs to the same class. It appears that central stimulation is most pronounced on administration of the sympathomimetic amines that do not have a phenolic hydroxyl group. No simple comparison can be made between the chemical structure of this class of drugs and that of cocaine.

SUMMARY

1. A state of catalepsy was produced in cats by the administration of bulbocapnine.

2. A state of excitement and stimulation of the sympathetic nervous system was produced by the administration of ac-tetrahydro-β-naphthylamine.

3. The cataleptic state produced by bulbocapnine was completely abolished by the administration of ac-tetrahydro-β-naphthylamine.

4. When bulbocapnine and ac-tetrahydro-β-naphthylamine were administered simultaneously in proper dosage, no symptoms characteristic of either drug appeared, the animal behaving in a normal manner throughout the period of observation.

Springfield State Hospital.

8. May, P.: The Chemistry of Synthetic Drugs, London, Longmans, Green & Co., 1918.

HISTAMINE CONTENT OF THE BLOOD DURING INSULIN SHOCK THERAPY

OTTO BILLIG, M.D.
ASHEVILLE, N. C.
AND
FREDERICK H. HESSER, M.D.
DURHAM, N. C.

Although insulin shock therapy has been widely accepted as an instrument in neuropsychiatric practice, knowledge is incomplete with regard to the physiology of the "shock" reaction. Beiglböck and Dussik,[1] Gellhorn,[2] Georgi [3] and others have discussed many of the more pertinent aspects of the subject, which is too extensive to be reviewed here. Consideration of certain features of insulin shock, together with what is known of the "histamine effect," suggested an investigation of the histamine content of the blood in patients receiving insulin shock therapy.

STUDIES OF HISTAMINE [4]

The blood of 6 psychotic patients well advanced under insulin shock therapy was tested for histamine at appropriate intervals during various clinically recognizable phases [5] of the hypoglycemic reaction. Venepunctures were done with reasonable care to avoid undue tissue injury. The tourniquet was always released before blood was withdrawn. Specimens were oxalated and refrigerated until extracted and assayed. Altogether, 14 series of quantitative determinations were carried out, according to the technic described by Code.[6]

METHOD

Extraction.—Ten cubic centimeters of whole blood is added to 15 cc. of 10 per cent trichloroacetic acid. The mixture is allowed to stand for thirty minutes and filtered by suction. The filtrate is treated with 10 cc. of concentrated hydrochloric acid and boiled for ninety minutes in an open Erlenmeyer flask. Water is added occasionally to prevent drying. The solution is evaporated to a final volume of 5 cc. Excess acid is removed by evaporating twice in the presence of 25 cc. of absolute alcohol over a water bath. The dried residue is extracted three times with 2 cc. of water, and the combined extracts are filtered. The filtrate is neutralized with a 10 per cent solution of sodium hydroxide, bromthymol blue being used as indicator. The extract is made up to 10 cc. with water.

Assay.—The histamine concentration in each extract was determined by comparing its capacity for stimulating contraction in an isolated portion of the lower portion of the ileum of the guinea pig with that of a standard consisting of Tyrode's solution containing 0.25 micrograms of histamine dihydrochloride per cubic centimeter. A 3 to 4 cm. section of intestine from an adult animal was kept at constant temperature (37.6 C.) for a half-hour in aerated Tyrode's solution containing 1 microgram of atropine sulfate per cubic centimeter. The intestine was then connected to a light lever registering on a centimeter scale and was suspended in a bath containing 8 to 10 cc. of Tyrode's solution under the same conditions of temperature and aeration. Consistent responsiveness was ascertained by repeated tests with the standard solution. Thereafter titration proceeded, a variable quantity (usually 0.05 to 0.5 cc.) of unknown solution being alternated with a constant dose (0.1 or 0.2 cc.) of standard solution to produce uniform contractions. The maximal response in each determination was read in centimeters of deflection from a resting level. Assays were carried out according to a definite time schedule, regular intervals being alloted for addition of material, reading and rest. It was found that the

From the Highland Hospital, Asheville, N. C., and the Department of Neuropsychiatry, Duke University School of Medicine, Durham, N. C.

1. Beiglböck, W., and Dussik, T.: Physiology of the Hypoglycemic Shock, Am. J. Psychiat. (supp.) **94**:50 (May) 1938.

2. Gellhorn, E.: Autonomic Regulations, New York, Interscience Publishers, 1943.

3. Georgi, F.: The Problem of Convulsions and Insulin Therapy: I., Am. J. Psychiat. (supp.) **94**:67 (May) 1938.

4. Dr. Frederick Bernheim, of the department of physiology of Duke University, provided material and advice as these studies progressed. Technical assistance was contributed by Mr. Philipp Deweese, who made most of the determinations of histamine, and by Mr. Robert L. Blake, who helped draw the figures. Dr. R. J. Floody (Hoffmann-La Roche, Inc., Nutley, N. J.), supplied us with histamine dihydrochloride (1:1,000).

5. These phases were recognized as (1) subshock, in which no loss of consciousness occurs, during a period corresponding to Frostig's (Am. J. Psychiat. **96**:1167 [March] 1940) first two "insulin hours" (suppression of cortical and cerebellar activity); (2) medium shock, in which consciousness is lost in accordance with the status in Frostig's third and fourth "insulin hours" (third hour, release of the basal ganglia and hypothalamus; fourth hour, release of the midbrain and suppression of pyramidal function), and (3) deep shock, marked by reduction of activity essentially to the level of the brain stem, during an interval corresponding to Frostig's fifth "insulin hour" (release of the medulla oblongata).

6. Code, C. F.: (*a*) The Quantitative Estimation of Histamine in the Blood, J. Physiol. **89**:257 (April 9) 1937; (*b*) The Source in the Blood of the Histamine-Like Constituent, ibid. **90**:349 (Aug. 17) 1937.

intestine remained consistently active if it was properly washed, aerated and relaxed (weight of lever suspended) before each test.

RESULTS

The results of our studies are shown in the accompanying charts (figs. 1 and 2), illustrating the concentration of histamine in the blood, expressed in micrograms per cubic centimeter, determined before insulin was given and during various phases of the insulin reaction.

Typical changes in the histamine level of the blood of a patient who finally went into deep shock are shown in *A* (fig. 1). Clinical signs which developed in the course of the reaction are noted. It is clear that the maximal concentration of histamine was found during the period of deepest shock.

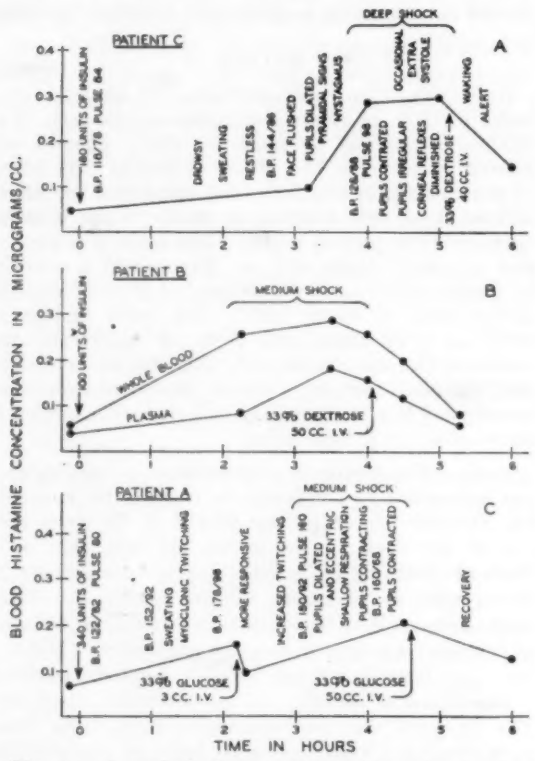

Fig. 1.—*A*, typical changes in the histamine level of the blood of a patient who finally went into deep shock. Various clinical data are noted on the chart. *B*, comparison of the histamine concentration of whole blood with that of plasma in a patient exhibiting "medium shock." *C*, alterations in the histamine level of the blood and the depth of shock effected by the administration of a small amount of dextrose to a patient who finally went into medium shock.

In *B* are shown values for 1 of 2 patients for whom the concentration of histamine in whole blood was determined, together with the concentration in the plasma from the same samples of blood. However, this comparison did not include a coincident determination of the cell-plasma ratio, which would have permitted an evaluation of the histamine content of the cells and of the plasma and would have taken into account a possible dehydration factor. Apparently, the histamine concentration of the plasma is less than that of whole blood, increases less rapidly and returns toward normal a little more promptly.

Alterations in the histamine level of the blood and in the depth of shock effected by the administration of a small amount of dextrose are demonstrated in *C*. At the beginning of the third hour, 3 cc. of a 33 per cent solution of dextrose was given intravenously to a patient

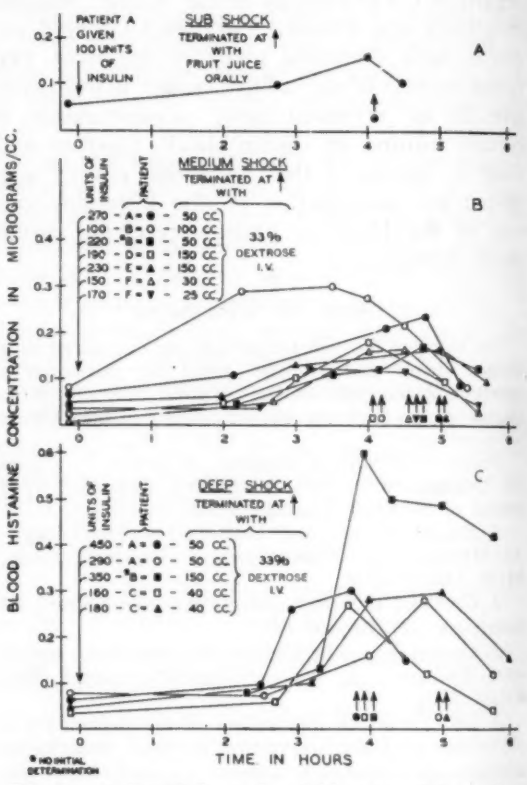
PATIENT A GIVEN 100 UNITS OF INSULIN
SUB SHOCK
TERMINATED AT WITH FRUIT JUICE ORALLY
A
MEDIUM SHOCK
TERMINATED AT WITH
UNITS OF INSULIN
PATIENT
270 - A = ● - 50 CC.
100 - B = ○ - 100 CC.
220 - B = ■ - 50 CC.
190 - D = □ - 150 CC.
230 - E = ▲ - 150 CC.
150 - F = △ - 30 CC.
170 - F = ▼ - 25 CC.
33% DEXTROSE I.V.
B
DEEP SHOCK
TERMINATED AT WITH
450 - A = ● - 50 CC.
290 - A = ○ - 50 CC.
350 - B = ■ - 150 CC.
160 - C = □ - 40 CC.
180 - C = ▲ - 40 CC.
33% DEXTROSE I.V.
C
BLOOD HISTAMINE CONCENTRATION IN MICROGRAMS/CC.
* NO INITIAL DETERMINATION
TIME IN HOURS

Fig. 2.—*A*, *B* and *C*, results of 13 series of determinations of histamine for 6 patients, presented according to the depth of clinical shock reached in each case. Various details are outlined on the charts and elaborated in the text.

entering medium shock, with an increased histamine level of the blood. Five minutes later the histamine concentration of the blood was lower and clinical "shock" less intense. Subsequently, the histamine concentration rose to its highest level during the period of deepest shock and fell again after treatment was interrupted.

In figure 2 the results of 13 series of determinations of histamine on our 6 patients are presented according to the depth of clinical shock reached in each patient. A small, but definite,

rise in the histamine level of the blood in a patient in whom "subshock" was terminated by oral administration of fruit juice at the beginning of the fifth hour is shown in *A*.

Seven superimposed histamine curves obtained from 5 of the patients whose reactions never exceeded medium shock are given in *B*. For 2 patients (patient B, receiving 100 units of insulin, and patient *F*, receiving 170 units of insulin), values for histamine fell slightly before shock was terminated. Each patient showed a concomitant spontaneous lessening of clinical shock. For every other patient the peak of the histamine curve coincided with the greatest depth of clinical shock just before the reaction was terminated by intravenous administration of dextrose. Values for histamine were observed to have returned to or toward normal in all patients an hour or more after the reaction was interrupted.

Five series of histamine determinations carried out on 3 of the patients whose reactions progressed into deep shock are outlined in *C*. Again, for each patient, the highest histamine level was observed during deepest shock, and prior to interruption of treatment. An unusual histamine response, with a pronounced rise and a slow fall in concentration, occurred in patient *B*, studied during the first treatment following a two weeks' interruption in the course of therapy. The more pronounced increase in histamine concentration here might be related to the phenomenon of "insulin sensitization."

From a comparison of *A*, *B* and *C* (fig. 2) it is evident that the concentration of histamine in the circulating blood parallels the intensity of clinical shock and that maximal values for histamine are found during deep shock.

COMMENT

Workers familiar with insulin shock therapy generally agree that the intensity of shock cannot be compared quantitatively with the insulin dose or with the level of the blood sugar. Georgi demonstrated this point conclusively in a series of 450 determinations of the blood sugar on patients receiving insulin therapy. He found that the most rapid fall in blood sugar occurred within the first half-hour after the administration of insulin and was accompanied by none of the so-called hypoglycemic phenomena. The lowest sugar level in the blood was usually reached in the third half-hour after injection, without regard to the dose of insulin. During the second hour, or at the beginning of the third hour, the blood sugar rose spontaneously and frequently reached twice the lowest level. Often, this rise in blood sugar paralleled the appearance of so-called hypoglycemic symptoms.

The behavior of patients under insulin therapy is often unpredictable, and management depends largely on the clinical course of the shock reaction. The latter, in turn, must be determined by a host of interdependent, and perhaps physiologically recognizable, factors other than those directly related to hypoglycemia. Among these factors may be included our own observations, which, though limited, point to a parallelism between the depth of shock, judged clinically, and the concentration of histamine (or histamine-like substances) in the circulating blood. As the intensity of the insulin reaction increased, the histamine level rose and attained maximal amplitude during deepest shock. After therapy was interrupted by the intravenous administration of dextrose, histamine values returned toward normal.

Haworth and MacDonald [7] found that the histamine level in whole blood of normal human subjects ranged from 0.018 to 0.78 microgram (average 0.04 microgram) per cubic centimeter. Code and MacDonald [8] described levels of from 0.05 to 0.11 microgram per cubic centimeter. Our average value was 0.045 microgram per cubic centimeter for whole blood before the administration of insulin. The greatest concentration of histamine was reached during deepest shock, and just before termination of the insulin reaction, in all but 2 patients. In each of these 2 subjects clinical signs of shock had begun to regress spontaneously before therapy was interrupted.

The histamine concentration of plasma was followed in 2 patients and apparently fluctuated in a curve similar to that of whole blood, although quantitatively the changes were less pronounced. According to Rose and Weil,[9] histamine is rapidly removed from plasma by the tissues, where it is inactivated. Conceivably, as insulin shock progresses, histamine in the plasma increases faster than the tissues can remove it and may eventually produce irreversible vascular changes. In this connection, the importance of further studies of histamine in relation to circulatory changes in the more severe complications of insulin shock is evident. The development of protracted shock includes the appearance of vascular phenomena having many characteristics

7. Haworth and MacDonald, A. D., cited by Code and MacDonald.[8]

8. Code, C. F., and MacDonald, A. D.: The Histamine-Like Activity of Blood, Lancet **2**:730 (Sept. 25) 1937.

9. Rose, B., and Weil, P.: Blood Histamine in Rabbit During Anaphylactic Shock, Proc. Soc. Exper. Biol. & Med. **42**:494 (Nov.) 1939.

in common with "histamine shock," i. e., peripheral collapse and circulatory failure.

In our series, the highest values for histamine in the blood varied between 0.122 and 0.612 microgram per cubic centimeter, with an average of 0.25 microgram per cubic centimeter at all shock levels. This is an increase of 456 per cent over our average preshock histamine level (0.045 microgram per cubic centimeter). The average value for histamine in the blood determined during deep shock only was 0.353 microgram per cubic centimeter (an increase of 684 per cent). During the first two hours after administration of insulin there was a slow increase in concentration of histamine. A more rapid increase continued during the third hour and the maximal histamine concentration coincided with a characteristic change in the clinical picture; i. e., shock progressed into the "medullary" phase. If the patient remained in "medullary shock" without further complication, a high histamine level persisted essentially unchanged. Spontaneous or induced fluctuations in the depth of shock were found to be accompanied by corresponding changes in the histamine level (figs. 2 *B* and 1 *C*).

Certain features in the clinical course of the insulin shock reaction suggest initial epinephrinemia, followed by a reversal of this effect as shock progresses. Increased pulse rate and blood pressure, sweating, dilated pupils and exophthalmos are frequently observed during the third hour after an appropriate dose of insulin. As shock deepens, the pulse rate decreases; the blood pressure falls to its original level; the pupils contract, sometimes to pinpoint size, and exophthalmos subsides.

Dale [10] suggested that secretion of epinephrine is an important factor in the normal resistance to histamine and showed that a small dose of histamine accelerates the secretion of epinephrine in the normal animal. He demonstrated that if infusion of large doses of histamine caused a strong epinephrine response, the symptoms of shock were "slight or evanescent." On the other hand, when signs of epinephrine response were less pronounced, symptoms referable to histamine were more severe, and recovery from the histamine reaction was delayed.

It is of interest to consider our data in relation to those of Heilbrunn and Liebert [11] on the epinephrine level of the blood serum during insulin hypoglycemia. Patients going into shock exhibited an inadequate epinephrine response to insulin ninety minutes after injection, whereas those presenting no evidence of coma displayed a pronounced rise in the epinephrine level of the blood at this time. During deep coma the epinephrine level was very low; on recovery it rose to a high level again. Our studies demonstrated that the histamine in the blood increases steadily as shock progresses and reaches its highest level at the time of deepest shock. Epinephrine and histamine have long been known to have certain antagonistic effects.

Anrep and Barsoum [12] showed experimentally that muscular contraction is accompanied by an increase in the histamine concentration in blood emerging from the active muscle. Whether histamine was liberated or produced by the muscles during their contraction was not determined. In our patients, the degree of restlessness during the shock reaction exhibited no direct relation to the level of histamine. Moreover, the highest histamine levels were observed during the relative inactivity of deep shock, and in 1 patient the histamine content of the blood decreased with returning motor activity. Again, these observations may be contrasted with those of Heilbrunn and Liebert [11] in their third group of patients. In this group the epinephrine level of the blood fluctuated considerably but was always low during deep coma. A high level of epinephrine was obtained, however, one-half hour after severe myoclonic twitchings developed.

Factors involved in the production, release and inactivation of histamine in the blood are poorly understood. Code [6a] showed that 90 per cent of histamine in the blood is carried in the white blood cells, especially in the eosinophilic leukocytes. Best and associates [13] demonstrated that histamine is present in the interior of living cells as long as the cell membrane is intact. Stimulation or injury of cells causes histamine to escape into the extracellular fluid. Georgi [3] suggested that insulin shock causes irritation of the cell membrane and an increase in the exchange of substances between the cell and its surroundings.

10. Dale, H. H.: Conditions Which Are Conducive to the Production of Shock by Histamine, Brit. J. Exper. Path. **1**:103 (April) 1920.

11. Heilbrunn, C., and Liebert, E.: Observations on the Adrenalin Level in the Blood Serum During the Insulin Hypoglycemia and After Metrazol Convulsions, Endocrinology **25**:354 (Sept.) 1939.

12. Anrep, C. V., and Barsoum, G. S.: Appearance of Histamine in the Venous Blood During Muscular Contraction, J. Physiol. **85**:409 (Nov. 22) 1935.

13. Best, C. H.; Dale, H. H.; Dudley, H. W., and Thorpe, W. V.: The Nature of the Vasodilator Constituents of Certain Tissue Extracts, J. Physiol. **62**:397 (March 15) 1927.

Code [6a] observed that histamine values return to normal within five to seven minutes after tissue injury. Weiss and associates [14] noted prompt recovery from single injections of histamine. Clinical recovery from an uncomplicated insulin shock, together with the return of histamine values to normal, may take an hour or more. This suggests that during insulin shock the inactivation rate of histamine is impaired in such a way that the removal of circulating histamine continues to be slow even after shock has been terminated and histamine is being released less rapidly.

From our studies, it would be difficult to decide whether the high level of circulating histamine results from increased release or decreased inactivation of histamine. However, a sequence, which may be represented schematically (fig. 3), is suggested. The histamine content of blood cells and plasma conceivably is held in equilibrium by the inactivating power of the tissues. The rate of removal of histamine from the plasma is influenced by many variables, including extent of the capillary bed, permeability of the capillary walls, arterial and venous blood pressures, cell-plasma ratio, fluid-electrolyte balance and complexity of tissue metabolism integrated through the nervous and endocrine system. The normal person has a capacity for inactivation of histamine which is ample for ordinary fluctuation in the histamine level of the blood. During insulin shock this capacity probably varies with individual tolerance, under the influence of the variables mentioned. As histamine is released more rapidly, changes occur first in the histamine content of the blood cells and are noted as an increase in the histamine content of whole blood without change in that of the plasma. (This in itself suggests the possibility that the additional histamine is released from tissue cells rather than from leukocytes and that the red blood cells take up this extra histamine as a protective mechanism.) When the liberation of histamine exceeds the rate of inactivation, the histamine concentration in the plasma increases; vascular changes are more pronounced; tissue edema occurs; the inactivating capacity of tissues is impaired, and the histamine level rises with corresponding rapidity. If the shock reaction is not terminated, protracted shock [15] (with more or less reversible vascular changes, depending on vascular reserve) may ensue. Hypothetically, histamine values would continue to rise according to the severity and duration of this reaction. If shock is interrupted by the

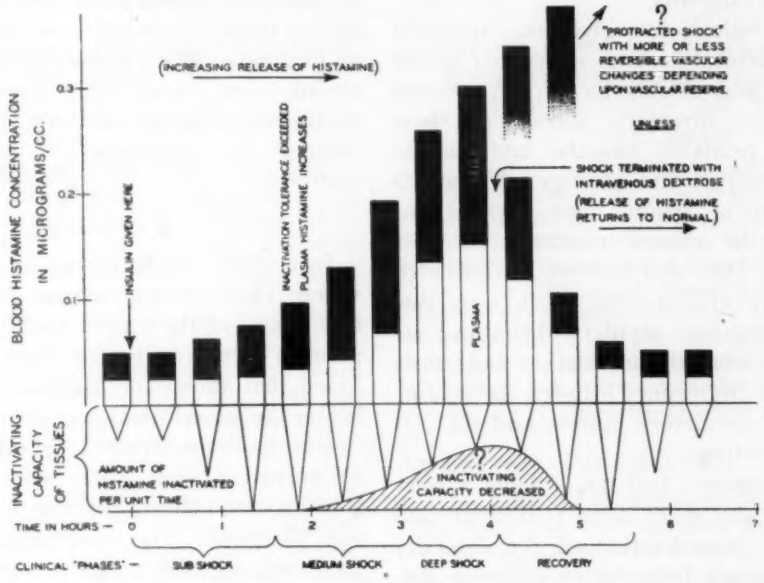

Fig. 3.—Schematic diagram suggested by the results of studies on the histamine content of the blood during insulin shock therapy. An effort has been made to illustrate changes in the histamine concentration of whole blood during various clinical phases of the insulin reaction, with attention to details elaborated in the text. The histamine concentration in the cells and plasma could not be plotted accurately because of limited material. It is likely that the histamine concentration in blood cells is actually greater than that shown.

14. Weiss, S., Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiaovascular System, Arch. Int. Med. **49**:360 (March) 1932.

15. Billig, O., and Sullivan, D. J.: Therapeutic Value of Protracted Insulin Shock, Psychiatric Quart. **16**:549 (July) 1942.

intravenous administration of dextrose, however, release of histamine returns to normal; the inactivating capacity of tissues is restored, and the histamine concentration of the blood falls to the preshock level as recovery takes place.

The striking similarity between activity in the terminal stages of fatal catatonia (Billig and Freeman [16]) and behavior during the later phases of insulin shock therapy, especially protracted shock, warrants closer investigation. Jahn and Greving [17] attributed the changes in fatal catatonia to an increase of "biogenous amines." By means of daily injections of large doses of histamine they were able to produce reactions in the experimental animal comparable to those in fatal catatonia.

When death follows hypoglycemia, structural changes in the central nervous system are rather typical (Sahs and Alexander [18]). Associated with stasis and thrombus formation, these alterations are primarily vascular and lead to secondary parenchymatous damage. Variations in the location of lesions may account for differences in the clinical picture. In their studies on cats, Dale and Laidlaw [19] concluded that the changes in histamine shock were due primarily to excessive capillary dilatation, escape of plasma from the circulation and stasis resulting from a discrepancy between the volume capacity of the circulatory system and the circulating blood volume.

Histamine possesses, perhaps, a wider variety of actions than any other drug (Goodman and Gilman [20]). In consideration of the diversity of its pharmacologic behavior in different animal species, it is hazardous to define the exact role of histamine whenever it appears in biologic processes. Any interpretation of the data presented, therefore, must be made with extreme care, in view of the metabolic complexity characterizing the insulin reaction.

Although we hope that these studies may eventually shed some light on the rationale in the management of complications in insulin shock therapy, no further statement can be made at present. The possibility of desensitization to histamine or the administration of histaminase in an attempt to reduce the risks of insulin shock may be considered, although the value of these methods in other fields is still unsettled. The effectiveness of ascorbic acid in combating histamine intoxication has been discussed by Unger and Bolger.[21] Ruskin [22] found that its effect was enhanced when the acid was combined in the form of calcium ascorbate. Recently, a number of workers, including Noble and Collip,[23] have produced evidence, now generally accepted, that adrenal cortical substance acts specifically to prevent histamine shock in the experimental animal. Desoxycorticosterone acetate completely protected adrenalectomized rats, which had become many times more sensitive than normal to histamine. Desoxycorticosterone acetate has already been shown to act favorably in cases of protracted shock and has been specifically recommended by Freudenberg [24] and von Braunmühl.[25]

SUMMARY

In a study of the histamine concentration in venous blood during various clinically recognizable phases of the insulin reaction in 6 psychotic patients receiving insulin shock therapy, it was found that values for histamine in whole blood before the administration of insulin corresponded closely to those reported by other investigators for normal persons. Early in the insulin reaction, a slight rise in the histamine level of the blood was observed. The concentration of histamine increased, together with the depth of shock, later in the insulin reaction, reached its peak during the period of deepest shock and returned toward normal after the reaction was interrupted by intravenous administration of dextrose. Values for the concentration of histamine in the plasma, though less than those for whole blood, apparently fluctuated in similar fashion. The average

16. Billig, O., and Freeman, W. T.: Fatal Catatonia, Am. J. Psychiat., to be published.

17. Jahn, D., and Greving, H.: Physical Disorders Accompanying Catatonic Stupor and Fatal Catatonia, Arch. f. Psychiat. **105**:105, 1936.

18. Sahs, A. L., and Alexander, L.: Fatal Hypoglycemia, Arch. Neurol. & Psychiat. **42**:286 (Aug.) 1939.

19. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, J. Physiol. **52**:355 (March) 1919.

20. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1942.

21. Ungar, G., and Bolger, M.: Prevention of Fatal Pulmonary Lesions from Inhalations of Irritant Vapors by Ascorbic Acid and by Histaminase, Comp. rend. Soc. de biol. **129**:1107, 1938.

22. Ruskin, S. L.: Influence of Vitamin C on the Antihistamine Action of Various Drugs, Arch. Otolaryng. **36**:853 (Dec.) 1942.

23. Noble, R. L., and Collip, J. B.: The Response of Normal, Hypophysectomized and Adrenalectomized Rats to Histamine Administration, Am. J. Physiol. **133**:623 (July) 1941.

24. Freudenberg, R.: Use of Vitamin B_1 and Preparations of Suprarenal Cortex in Insulin Shock Therapy, Am. J. Psychiat. (supp.) **94**:317 (May) 1938.

25. von Braunmühl, A.: Die Insulinshockbehandlung der Schizophrenie, Berlin, Julius Springer, 1938.

maximal increase in the histamine concentration of the blood was 456 per cent for all patients; the average maximal increase for patients in deep shock was 684 per cent. Changes in the histamine level corresponded to spontaneous fluctuations in the depth of shock. Administration of a small amount of dextrose intravenously to 1 patient reduced the depth of shock and the histamine level concomitantly. Comparison of histamine levels during subshock, medium shock and deep shock revealed that the concentration of histamine in the circulating blood apparently corresponded to the intensity of clinical shock observed during the insulin reaction.

CONCLUSION

Our studies indicate a parallelism between the depth of shock, estimated clinically during the insulin reaction, and the concentration of histamine (or histamine-like substances) in the circulating blood.

Highland Hospital, Asheville, N. C.

Department of Neuropsychiatry, Duke University, School of Medicine.

News and Comment

AMERICAN BOARD OF NEUROLOGICAL SURGERY

The following physicians were examined, passed and certified on June 5, 1944:

Dr. R. C. Buckley, Hartford, Conn.; Dr. DeWard Jones, United States Public Health Service, Los Angeles; Major Frank Lusignan, Medical Corps, Army of the United States; Dr. Jost J. Michelsen, Boston; Dr. Ignaz W. Oljenick, Baltimore; Captain J. H. Taeffner, Medical Corps, Army of the United States; Dr. J. L. Ulmer, Boston, and Commander D. H. Werden (MC), U.S.N.R.

The following physicians were examined and passed, and their certificates will be withheld until they have satisfied the board that they have satisfactorily completed two years of independent practice in neurologic surgery:

Lieutenant Harvey Chenault, Medical Corps, Army of the United States; Dr. Henry Cuneo, Los Angeles; Lieutenant (jg) James G. Galbraith (MC), U.S.N.; Lieutenant Edward B. Schlesinger, Medical Corps, Army of the United States; Captain Benjamin Whitcomb, Medical Corps, Army of the United States, and Dr. Henry T. Wycis, Philadelphia.

APPOINTMENT OF COMMISSIONER OF MENTAL DISEASES, OHIO STATE DEPARTMENT OF PUBLIC WELFARE

Dr. Frank F. Tallman has resigned the directorship of mental hygiene in the state of Michigan, which position he has held for two and one-half years, to accept the position of Commissioner of Mental Diseases in the State of Ohio Department of Public Welfare, Columbus, Ohio. The Division of Mental Diseases, which Dr. Tallman will supervise, comprises fifteen hospitals for the mentally ill, feebleminded and epileptic, with a population of about 27,000 patients. In addition to this work, Dr. Tallman will be responsible for a receiving hospital program and a state-wide program of mental hygiene.

AMERICAN PSYCHIATRIC ASSOCIATION

At the centennial meeting of the American Psychiatric Association, held in Philadelphia, May 15 to 18, 1944, the following officers were elected: president: Karl M. Bowman, M.D., San Francisco; president elect: Samuel W. Hamilton, M.D., Washington, D. C., and secretary-treasurer: Winfred Overholser, M.D., Washington, D. C.

CORRECTION

In the article by Alfred J. Kahn, Ph.D., entitled "Effects of Variations in Intracranial Pressure," in the June issue (ARCH. NEUROL. & PSYCHIAT. **51**:508, 1944), the following paragraph should be inserted in the second column on page 510, immediately after "Procedure" under Experiment 2:

> "Result: The animal remained in a comatose state and died several hours later."

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

RETICULOCYTOSIS FOLLOWING ABLATION OF FRONTAL CEREBRAL CORTEX. F. A. METTLER, Arch. Surg. **46**: 572 (April) 1943.

Mettler studied the effect of cortical excisions on the erythrocyte count, especially on the number of reticulocytes. Bilateral removal of the frontal cortex in dogs is followed by a pronounced increase in the reticulocyte count, which does not occur after ablation of other cortical areas. The reticulocytosis is not due to hemoconcentration. There seems to be a parallelism between reticulocytosis and increased gastric acidity after excision of the frontal cortex.

LIST, Ann Arbor, Mich.

THE MONKEY (MACACA MULATTA) AFTER HEMISECTION AND SUBSEQUENT TRANSECTION OF THE CORD. G. P. MCCOUCH, J. HUGHES and W. B. STEWART, J. Neurophysiol. **6**:155 (May) 1943.

McCouch, Hughes and Stewart performed hemisection of the spinal cord followed by complete transection in 15 monkeys. Recovery of reflexes always occurred more rapidly on the previously paretic side. In 3 animals stimulation of the acutely paretic side produced on the chronic side crossed reflexes, crossed flexion of digits in a few hours and crossed extension of the leg after two or more days. Crossed inhibition was sometimes more effective when driven from the chronic side. Asymmetry was only exceptionally reflected in internuncial potentials.

FORSTER, Philadelphia.

THE EFFECT OF INSULIN HYPOGLYCEMIA ON CONDITIONED REFLEXES. E. GELLHORN and H. MINATOYA, J. Neurophysiol. **6**:161 (May) 1943.

Gellhorn and Minatoya studied by means of conditioned reflexes the chronic effect of insulin hypoglycemia on the central nervous system. Normal rats which would jump across a partition to a neighboring compartment in response to electrical stimulation were conditioned to react in a similar manner to the sound of a bell. This response was inhibited by lack of reenforcement. Insulin hypoglycemia was found to restore the response. The number of administrations of insulin and the degree of hypoglycemia were observed to influence the disinhibiting effect. The induction of insulin hypoglycemia during the conditioning period increased the number of positive responses.

FORSTER, Philadelphia.

CORTICAL LOCALIZATION OF SYMBOLIC PROCESSES IN THE RAT: II. EFFECT OF CORTICAL LESIONS UPON DELAYED ALTERNATION IN THE RAT. C. T. MORGAN and W. M. WOOD, J. Neurophysiol. **6**:173 (May) 1943.

Morgan and Wood studied the behavior of rats in a T maze both before and after operation in order to determine whether there are limited areas of the anterior cortex subserving symbolic processes, especially recent memory. Their results indicated some localization of recent memory in the anterior areas of the rat brain, but the precise localization was not determined.

FORSTER, Philadelphia.

CLINICAL STEPS IN THE METABOLISM OF ALCOHOL BY BRAIN IN VITRO. JOHN G. DEWAN, Quart. J. Stud. on Alcohol **4**:357 (Dec.) 1943.

Dewan presents evidence that brain tissue and the liver possess similar mechanisms for oxidation of alcohol in that the vitamins nicotinic acid and riboflavin are present and the end result of oxidation is acetic aldehyde and acetic acid. He concludes that although the liver is the main site of the primary oxidation of alcohol, the brain tissue is capable of performing the same function, though to a lesser degree.

GUTTMAN, New York.

ACCELERATION OF CO-ORDINATED MUSCULAR EFFORT BY NICOTINAMIDE. I. M. FRANKAU, Brit. M. J. **2**: 601 (Nov. 13) 1943.

Frankau summarizes the results obtained from a series of carefully controlled experiments undertaken to demonstrate by means of a selected test the effect, if any, of certain vitamins on the physical efficiency and the fatigability of healthy young adults. The test used not only was severe but required complete cooperation from the subject. The results indicate that the addition of nicotinamide alone or with certain other vitamins to the diet of fit young men increased their efficiency in regard to physical effort and coordination. It was noted that continued heavy or exhausting physical stress might necessitate increasing the dose of nicotinamide.

ECHOLS, New Orleans.

Psychiatry and Psychopathology

PSYCHOLOGICAL OBSERVATIONS IN AFFECTIVE PSYCHOSES TREATED WITH COMBINED CONVULSIVE SHOCK AND PSYCHOTHERAPY. NORMAN A. LEVY and ROY R. GRINKER, J. Nerv. & Ment. Dis. **97**:623 (June) 1943.

Levy and Grinker believe that convulsive therapy in cases of melancholia and depressions serves to weaken the repressing cortical activity, so that repressed aggressive impulses are liberated and made accessible to dynamic psychotherapy. They report a number of cases in which the transference attitudes gained by the shock methods were utilized in this manner.

Case 1 was that of a woman aged 30 with intractable pain and obsessive interest in her teeth and gums; she was initially inaccessible to psychotherapy, but, after seven electrically induced convulsions, suddenly and dramatically began to express unrevealed conflicts based on a fear of pregnancy. Subsequent psychotherapy with a modified psychoanalytic technic succeeded after a number of months in bringing about a reasonably good adjustment, with the ego strengthened and better able to meet reality-testing situations. The patient's dependent needs decreased. In case 2, a dependent, narcissistic, perfectionistic woman with a depressive illness was enabled by a combination of metrazol treatments and

long-continued psychotherapy to develop a "new personality," with her repressed hostility externalized and socialized and its origin understood, and with the final attaining of conscious intellectual insight. In cases 3 and 4 shock therapy lifted depressive inhibitions, allowed ventilation of grievances and permitted factors of reality to be sufficiently manipulated so that adequate adjustments could be made. Cases 5 and 6 were representative of the group in which shock treatment was not accompanied by psychotherapy. In these cases the repressed aggressions were not overtly expressed, but found symbolic deliverance in dreams and fantasies.

The authors warn that the amount of shock therapy should be carefully regulated so that manic swings do not occur, since psychotherapy cannot be carried on during these states. This is illustrated in case 7.

Psychotherapy as an adjunct to convulsive therapy may permit the development of enough insight to prevent recurrence of depression, as was the situation in case 8.

CHODOFF, Langley Field, Va.

PROGNOSIS IN SCHIZOPHRENIA. LOUIS S. CHASE and SAMUEL SILVERMAN, J. Nerv. & Ment. Dis. **98**:464 (Nov.) 1943.

Chase and Silverman attempt to correlate the results of metrazol and insulin shock therapy with the prognosis, using as material 100 schizophrenic patients treated with metrazol and 50 schizophrenic patients treated with insulin. The prognosis for each of the 150 patients was made without prior knowledge of the results of treatment. The favorable prognostic signs of most importance were short duration of illness, acute onset, obvious exogenous precipitating factors, early prominence of confusion, atypical (especially manic-depressive) symptoms and minimal or no process symptoms. Factors of less significance were a history of previous attacks, pyknic body type, extrovertive temperament and illness of catatonic or atypical type. The presence of the converse factors was considered to indicate an unfavorable prognosis. Process symptoms included depersonalization, derealization, massive primary persecutory ideas and sensations of influence, conscious realization by the patient of disintegration of the personality, bizarre delusions and hallucinations, pronounced apathy and dissociation of affect. Of 43 patients for whom the prognosis was considered good, 77 per cent had remissions, while of 74 patients for whom a poor outcome was predicted, 85 per cent showed no improvement. In these two prognostic groups, there was no significant difference between those treated with insulin and those treated with metrazol. In the group of patients with "fair" prognoses, remissions were obtained in 32 per cent of those treated with metrazol and in 73 per cent of those treated with insulin. It was thus found that shock therapy shortens the duration of illness of patients with a favorable prognosis and may be the deciding factor in the recovery of those for whom the outcome is doubtful.

The importance of the prognostic criteria was weighed in the light of the results of treatment. The two most significant factors for a favorable outcome were short duration of illness (less than one year) and absence of process symptoms. Long duration of illness (more than two years) and presence of process symptoms (in the absence of confusion) were important criteria for an unfavorable prognosis. Other, less important, favorable prognostic indications were atypical acute symptoms, acute onset, obvious exogenous precipitating factors, previous episodes, an illness of catatonic or atypical type, pyknic habitus and extroversion. Pre-psychotic adjustment, onset under 40 years of age, sex and family history were factors of little value for prognosis.

CHODOFF, Langley Field, Va.

SOME ASPECTS OF MIND IN ASTHMA AND ALLERGY. ETHAN ALLAN BROWN and LIONEL GOITEIN, J. Nerv. & Ment. Dis. **98**:638 (Dec.) 1943.

Brown and Goitein review briefly the literature on the psychiatric and nervous elements in bronchial asthma. They assert that little attention has been paid to the main personality in its more detailed structure in relation to the symptom. In many instances vague traits, rather than precise personality stratums, have been considered. In the present paper a group of asthmatic patients, another group of nonasthmatic allergic patients and a control group of healthy nurses and students were studied with the purpose of evaluating the normal personality makeup and the degree of mental integration. The procedures used included psychologic biotyping, objective testing, direct questioning and psychiatric interviews carried out by the indirect method and the technic of "associative anamnesis."

A high percentage of the patients with asthma were of a specific character type. This was of the constrained order, such as is observed in persons with obsessive psychoses, with a conative secondary function and a mental attitude of magnanimity. The asthmatic patients also showed equanimity of mood, but with definite indications of repressed instincts of hate and more manifest instincts of ambitious drive for ascendancy. Most of the patients conformed to a biotype best described as reflex and reactive and, physically, were of the pyknosomatic type. As a group the asthmatic patients were partly fixated at pregenital levels of development. Of the 40 asthmatic subjects, 8 showed a significant neurotic disturbance, and 9, distinctive character anomalies of a specific tendency. Twelve per cent of the patients presented phobic trends as severe as those associated with true obsessions. The hypomanic reaction and repressed guilt, narcissism, anxiety and masochism were also represented.

The asthmatic subject is of a cyclothymic disposition with associated paranoid features, repressed hostility and motives of self punishment. The authors believe that this pattern comprises a specific entity, the "respiratory personality."

CHODOFF, Langley Field, Va.

A STUDY OF WOMEN WITH PSYCHOPATHIC PERSONALITIES REQUIRING HOSPITALIZATION. R. J. VAN AMBERG, Psychiatric Quart. **18**:61 (Jan.) 1944.

Van Amberg studied 34 women with psychopathic personalities. He defines the psychopathic personality as one "who [is] not ill in a neurotic or psychotic sense, but who [is] struggling with difficult life-adjustments, often requiring mental hospital care for functional disturbances and antisocial behavior."

Each patient was questioned for details of her family life, her adjustments at school, her social relationships and her sexual maturity.

The patients were divided into four types: (1) the grossly inadequate and antisocial personality ("the usual psychopath"); (2) the overindulged and emotionally immature person, who cannot meet the usual responsibilities of adult life; (3) the almost adequate personality,

adequate only so long as things go fairly well, and (4) the sexually maladjusted patient, with a "rather solid social personality."

Treatment consisted chiefly in psychotherapy. The patients of the first type, 5 women, did not improve on hospitalization, and the only good result of their stay was the temporary relief it may have afforded their families. Of the 15 overindulged women, who did not show symptoms until faced with responsibility, 4 "did rather well after leaving the hospital." Two of the 5 with "almost adequate" personalities made limited adjustments after leaving, and 1 did very well. The author stated that 4 of the 9 sexual psychopaths did rather well after their stay at the hospital.

The author concludes that patients of the last two types have fairly sound personalities and their prognosis is better than the prognosis for patients of the first two types. Alcohol may play a contributing part in precipitation of any of the illnesses; in some cases it is the only factor that releases the symptoms.

McCarter, Philadelphia.

Neurotic and Psychiatric States as Causes of Inability to Work in England, 1940-1941. Howard E. Collier, Brit. M. J. **2**:461 (Oct. 9) 1943.

Collier undertook a study of 2,000 records from a large industrial insurance company in England for 1940 and 1941 in an effort to determine: (1) the actual incidence of neurotic and psychiatric illness, (2) the relative importance of the "nervous factor" in delaying recovery from illness and (3) the probable incidence of major psychiatric disability. From this analysis he concluded: (1) About 280 in every 1,000 disabled persons are likely to experience an unduly prolonged disablement by reason of "nervous disorders"; (2) the ratio of nervous illness is greater in women than in men, in the proportion of 320:246, and (3) the social status apparently is not a distinguishing factor in the incidence of nervous disorders. He estimated the maximum rate of psychiatric disorders in the population as follows: 7.6 per 1,000 insured persons will be disabled by neuroses; the disablement of 2.4 per 1,000 persons will be due to neuroses, and 3 per 1,000 disabled persons will require expert psychiatric assistance.

Echols, New Orleans.

Ocular Manifestations of Neuroses Commonly Found Among Soldiers. I. C. Michaelson, Brit. M. J. **2**:538 (Oct. 30) 1943.

Many soldiers react to chronic anxiety by manifesting a neurosis, of which there are two main varieties: hysteria and the chronic anxiety state. As a result of such psychic conditions, there may arise various ocular complaints, such as defective day or night vision, asthenopia, headache, photophobia, spots before the eyes and epiphora, all of which are of functional origin. Michaelson calls attention to the fact that in practice the neurosis usually does not follow a clearcut pattern. Furthermore, the same patient may have one psychic disturbance superimposed on another, or organic and functional disorders may be present in the same person. For these reasons, the importance of a thorough physical examination cannot be too strongly emphasized. He states that the treatment of chronic anxiety state with ocular manifesations is more satisfactory than is that of hysteria with ocular disturbances. In most instances the patient responds intelligently and emotionally to treatment by the ophthalmologist who listens patiently and kindly to his story and is direct in explaining to him how his symptoms arose.

Echols, New Orleans.

Anxiety States in the Navy. G. V. Stephenson and Kenneth Cameron, Brit. M. J. **2**:603 (Nov. 13) 1943.

Stephenson and Cameron report their impressions obtained from a study of 1,300 men with anxiety states whom they treated at a Royal Navy Hospital during 1940 and 1941. They believe that the basic condition is anxiety in its psychosomatic manifestations and that it is this reaction which is regarded as releasing the varied psychotherapy of the constitution affected. The anxiety state with disability develops in three stages, which the authors describe as "early stress," "established tension" and "anxiety with exhaustion." However, in practice the picture is mixed; manifestations may be psychic, somatic or mixed and vary from mild disturbances of function to gross hysterical features. From their study the authors noted that in the average stable person there is a remarkable capacity for recovery from anxiety states. Almost all the patients in their series were able to return to some form of service.

Echols, New Orleans.

Meninges and Blood Vessels

The Recognition of Meningococcic Infections. Paul S. Strong, Am. J. M. Sc. **206**:561 (Nov.) 1943.

Strong believes that a petechial rash occurs frequently in cases of epidemic meningitis (82 per cent). The specific rash of meningococcemia is always hemorrhagic and cannot be obliterated by pressure, becoming manifest before the first twenty-four hours of infection. It reaches its full development within a few hours and fades rapidly. An almost invariable feature of the infection is the sudden onset of the disease, frequently in less than six hours. An infection of the blood stream is suggested by chills, fever, drowsiness, headache, pallor and pains in the limbs. Severe, intractable headache is present in 94 per cent. Disturbances of consciousness range from mild drowsiness to extreme coma, with signs of meningeal irritation, especially nuchal rigidity. Thirty cases in Strong's series were recognized before there were clinical signs of meningeal involvement. In 4 out of 20 cases in which spinal puncture was performed the cell count ranged from 8 to 27 cells per cubic millimeter of fluid. Forty of the 90 blood cultures were positive for Neisseria intracellularis. In 23 instances meningococci were grown from both the blood and the spinal fluid. Seven cases of arthritis were encountered.

Michaels, Martinsburg, W. Va.

Meningococcemia. Eugene P. Campbell, Am. J. M. Sc. **206**:566 (Nov.) 1943.

Campbell presents a clinical report of 3 new cases of meningococcemia and an analysis of 85 cases of the prolonged form of the disease collected from the literature. Various concepts of pathogenesis, from direct extension to distribution by the blood stream, are reviewed. It is likely that the usual route of invasion is by the blood stream. The author records the cases of 3 youths (17, 18 and 20 years of age) with meningococcemia who recovered after treatment respectively with sulfapyridine,

in the first case, with sulfanilamide, in the second case, and with a combination of antimeningococcic serum and sulfanilamide, in the third case.

Analysis of the clinical characteristics of 88 cases of meningococcemia revealed that the condition involved 60 males (69 per cent), 20 (33 per cent) of whom were 20 to 29 years of age. The incidence in the third decade was nearly twice as great as one would expect. The average duration of the illness from onset of symptoms to recovery was eleven and two-tenths weeks, with extremes of two to one hundred and twenty weeks. There was no predominant seasonal incidence. Fever, rash, arthralgia, chills and headache constituted the five important features. Sore throat was noted in only 9 cases. Herpes labialis occurred infrequently (5 cases). In 10 cases (11.4 per cent) there was no mention of rash. The rash varied from a sparse petechial to a diffuse eruption. Generalized aches and pains in the joints and back were prominent features. Meningitis occurred as a complication in 25 cases. It was a bad prognostic sign, and the outlook was most serious when meningitis occurred in the older age groups. Endocarditis was thought to be a complication in 13 cases (15 per cent), in 4 of which death occurred. Nephritis was reported in 8 cases, in 5 of which the patients were in the first two decades of life. Cultures of the meningococcus were obtained from each of the 88 patients, some with difficulty. The most favorable results were obtained with chemotherapy. MICHAELS, Martinsburg, W. Va.

ASEPTIC CAVERNOUS SINUS THROMBOSIS WITH RECOVERY. H. S. LE MARQUAND and E. G. RECORDON, Lancet **1**:247 (Feb. 19) 1944.

Le Marquand and Recordon report the case of a man aged 29, who received a hard blow over the right eye from a soccer ball, resulting in a momentary blackout. Six days later he had a sore congested pharynx; hemolytic streptococci were grown from material from the throat, and he was given sulfapyridine (8 Gm.). Five days later he had signs of bilateral thrombosis of the cavernous sinus, the temperature not reaching over 99.4 F. then or later and no meningeal signs appearing. Sulfapyridine and sulfathiazole were given (10 and 15 Gm. respectively), and three days later the signs started to subside. Cultures of the blood and spinal fluid were negative, as was the urine.

The authors did not feel that a completely satisfactory explanation was possible. Either the blow to the head or the infection of the throat caused rapidly spreading thrombosis. One month after the original trauma recovery was complete except for some residual retinal disturbance in the right eye.

McCARTER, Philadelphia.

Diseases of the Brain

CALCIFIED SUBDURAL HEMATOMA. DAVID A. BOYD JR. and PAUL MERRELL, J. Nerv. & Ment. Dis. **98**:609 (Dec.) 1943.

In the event that a subdural extravasation of blood does not prove fatal and is not removed surgically, it tends to organize into a fibrous envelope containing disintegrating blood clot. In the course of several years the wall may become hyalinized, and in rare cases calcified and ossified. Boyd and Merrell report a case of chronic subdural hematoma with a probable duration of twenty-six years. Roentgenograms revealed a sharply demarcated, "shell-like" mass beneath the right parietal portion of the skull, with irregular calcification of its outer surface. This was removed surgically.

The authors discuss the difference in roentgenographic appearance in cases in which the trauma occurred in infancy and in cases in which it occurred in adult life. In the former there is enlargement of the skull on the side of the lesion, with elevation of the sphenoid ridge and deepening of the middle fossa. In the latter usually no changes are visible in the plain roentgenogram, although they were present in the case reported.

In the usual case, calcification does not begin until the third year after the injury, but there is considerable individual variation. Operative removal of calcified subdural hematoma is not difficult, owing to the lack of vascularity, but a stormy postoperative course may be expected as a result of the extensive edema of the brain following the release of pressure.

CHODOFF, Langley Field, Va.

DEATH DURING SULFONAMIDE TREATMENT. OSCAR POLLAK and JOSEPH ZISKIND, J. Nerv. & Ment. Dis. **98**:648 (Dec.) 1943.

The toxic effects on the brain of the sulfonamide compounds described in the literature have been mainly vascular. It has been noted that patients with lupus erythematosus and arthritis, or with acute rheumatism, are especially susceptible to the effects of the drugs. Pollak and Ziskind report the case of a child aged 14 with disseminated lupus erythematosus who died under treatment with sulfanilamide and sulfathiazole. Postmortem examination of the brain revealed numerous thrombi, which caused perivascular disintegration. Some of these thrombi were composed of masses of necrotic cells, similar to those observed outside the blood vessels. Since there was also severe hepatitis, with liver cells lying free in the hepatic vessels, the authors conclude that the cells in the brain were liver cells which had been transported through the vascular system. This phenomenon has been observed previously in experimental animals in the presence of severe damage to the liver. CHODOFF, Langley Field, Va.

THE PROGNOSIS IN CIVILIAN HEAD INJURIES. E. GUTTMAN, Brit. M. J. **1**:94 (Jan. 23) 1943.

Guttman examined 300 patients admitted consecutively with head injuries from the standpoint of the effect of psychologic factors on the prognosis. Of these, 255 patients whose records were available for analysis were studied in detail. Ten patients (4 per cent) died, and 2 were permanently disabled because of cerebral damage. All were treated by an active method of early rehabilitation. Over 80 per cent of the hospitalized patients left in two weeks. The average duration of absence from work was about eight weeks. Patients with mild disturbances, with post-traumatic amnesia of one hour or less, were absent from work four to five weeks; patients with injuries of moderate severity, with post-traumatic amnesia of one to twenty-four hours, five to six weeks; patients with severe injuries, with post-traumatic amnesia of one to seven days, about nine weeks, and patients with the severest injuries, fourteen weeks. Guttman noted that when a patient remained away from work an unusually long time social and psychologic, rather than physical, factors were involved. This, he believes, emphasizes the necessity for early psychologic management and after-care of patients with head injuries. ECHOLS, New Orleans.

AGE INCIDENCE AND PROGNOSIS OF EPILEPSY. F. J. NATTRASS, Brit. M. J. **2**:481 (Oct. 16) 1943.

Because Nattrass' experience had been contrary to the general observation that idiopathic epilepsy rarely has its onset in later life, he undertook a study of 602 patients seen over a period of eighteen years. He found that 25 per cent of the patients showed the first evidences of epilepsy after the age of 30 and 13 per cent after the age of 40.

The 61 patients in whom epilepsy developed after the age of 40 were followed up in an effort to determine the cause of the attacks and the prognosis. Adequate information could be obtained on 41 of these patients. None showed signs of intracranial tumor, and there was no greater incidence of arteriosclerosis in this group than in nonepileptic population. These patients showed a tendency to decrease in the frequency and severity of attacks with the passage of time. Epilepsy developing after the age of 30 has remarkably little effect on the patient's mental or general physical condition.

ECHOLS, New Orleans.

THE BACTERIOLOGY OF BRAIN ABSCESS. ALLAN M. MCFARLAN, Brit. M. J. **2**:643 (Nov. 20) 1943.

McFarlan reports the bacteriologic observations in 48 cases of cerebral abscess seen in neurosurgical clinics. Staphylococcus aureus, the commonest organism, was present in 15 of the 48 cases. The next in the order of frequency were the fusiform bacilli and the anaerobic streptococci, each of which were noted in 10 cases. Streptococcus pneumoniae, Proteus vulgaris and Streptococcus pyogenes were isolated in several cases. McFarlan calls attention to the fact that several authors have considered the streptococcus as the commonest offender, but the results of culture in his series suggest that several species may have been represented. For this reason, he believes that anaerobic culture should be an essential part of the examination of pus from an abscess of the brain. In 33 cases only one organism was found; in 14 cases more than one organism was recovered, and in 1 case the specimen was sterile. Because of insufficient data, it was impossible to draw any conclusions about the time relations of capsule formation or to compare the speed of encapsulation of abscesses due to different organisms. Although it has been repeatedly stated that anaerobic and gram-negative bacilli inhibit capsule formation, there were 2 cases in the author's series in which fusiform bacilli was isolated and the abscess was shown histologically to be well encapsulated; this was also true in 2 cases of abscess from which P. vulgaris was isolated.

ECHOLS, New Orleans.

ENCEPHALOMYELITIS FOLLOWING VACCINATION IN FIFE. G. MATTHEW FYFE and J. B. FLEMING, Brit. M. J. **2**:671 (Nov. 27) 1943.

During the epidemic of smallpox in Fife County, Scotland, in 1942, 9 cases of vaccinial encephalomyelitis occurred among a group of 75,326 recently vaccinated persons. All the patients were children. There were 4 deaths. The symptoms were suggestive of encephalitis in 6 children, of myelitis in 2 children and of lymphocytic meningitis in 1 child. Administration of parental immune serum in large doses was effective in treating the patients with the more serious conditions. Fyfe and Fleming believe that the success of the treatment suggests that a virus of vaccinia is the etiologic factor in postvaccinial encephalitis. He also noted that most of his patients showed evidence of acute infection of the upper respiratory tract. Because postvaccinial encephalitis is extremely rare in infancy, the best time for vaccination is during this period.

ECHOLS, New Orleans.

Treatment, Neurosurgery

TREATMENT OF MENINGOCOCCUS CARRIERS WITH SULFADIAZINE. F. S. CHEEVER, B. B. BREESE and H. C. UPHAM, Ann. Int. Med. **9**:602 (Oct.) 1943.

Cheever and his associates report an outbreak of meningococcic infections in a large naval construction training center during the winter of 1942-1943. Patients with uncomplicated septicemia were observed; in over 90 per cent of the patients a type I meningococcus proved to be the causative organism. The response to sulfadiazine therapy was gratifying; the mortality rate remained about 5 per cent. Determination of the carrier rate for a representative sample of the camp's population gave a total incidence of 57.6 per cent. Men from a barrack known to have a high carrier rate were divided into two equal groups. These men lived, worked and messed together. On the first day cultures of material from the nasopharynx were made from all the men; the subjects in the first group were given 3 Gm. of sulfadiazine in divided doses on the first day, and similarly, 3 Gm. on the second day and 2 Gm. on the third day, each man receiving a total of 8 Gm. in seventy-two hours. The second group, serving as a control, was not treated. On the fourth day cultures were made again in both groups, and specimens of nine were obtained from men who had received the drug. On the seventh day another culture of material from the nasopharynx was made for each man. Cultures of 161 carriers given 8 Gm. of sulfadiazine had become negative by the fourth day. After an additional three days, during which no treatment was given, 160, or 99.51 per cent, had negative cultures. The control group receiving no treatment showed a statistically significant increase in the total carrier rate during the first seventy-two hours and a slight decrease during the second seventy-two hours. Sulfadiazine is apparently fully as effective as other members of the group of sulfonamide compounds in the treatment of meningococcus carriers.

J. A. M. A.

REPAIR OF LARGE CRANIAL DEFECTS. V. S. LAMBROS, Arch. Surg. **46**:575 (April) 1943.

Lambros reports the case of a man aged 26 who had a meningioma in the right frontoparietal region, with a large area of hyperostosis of the overlying portion of the skull. At the first operation the tumor and the hyperostotic bone were completely excised, and the dural defect was repaired with a free graft of fascia lata. At a second operation the extensive defect of the skull was covered by three pieces of bone from the outer table of the patient's ilium. The cosmetic result was excellent, but a limp, due to weakness of the gluteal muscles, was present for several months. Furthermore, roentgenograms taken six months after operation revealed mild resorption of the bony grafts.

Other methods of repair of large cranial defects are discussed. Several good nonosseous substances are available: metals, such as vitalium and tantalum, or plastics, such as methyl methacrylate. All these materials are nonresorbable and give good protection and excellent cosmetic results, but they tend to produce some irritation of tissues and may thereby predispose to infection.

LIST, Ann Arbor, Mich.

SPREADING OSTEOMYELITIS OF THE FRONTAL BONE TREATED WITH PENICILLIN. H. L. WILLIAMS and D. R. NICHOLS, Proc. Staff Meet., Mayo Clin. **18:** 467 (Dec. 1) 1943.

Williams and Nichols report on the successful treatment of 2 patients with spreading osteomyelitis of the frontal bone. Both patients had received apparently adequate doses of sulfadiazine or sulfathiazole, without control of the infection. There was a prompt favorable response to penicillin. In 1 of the patients a subperiosteal abscess, associated with an epidural abscess, was subsequently treated surgically.

GUTTMAN, New York.

THERAPY OF OPTIC NEURITIS WITH NICOTINIC ACID. S. BARRENECHEA and others, Ophth. ibero am. **5:**7, 1943.

Barrenechea and his collaborators employed nicotinic acid in 5 cases of optic neuritis. The disease was retrobulbar in 4 cases. It was of alcoholic origin in 2 cases, due to focal infection in 2 cases and secondary to mumps in 1 case. The substance was administered by mouth in doses of 50 mg. each six times a day, up to a daily total dose of 300 mg. for ten consecutive days. In the course of the first twenty-four or forty-eight hours central vision and visual field improved, the central scotomas disappeared and the subjective symptoms stopped. The author believes that optic neuritis, whether retrobulbar or not, is due to local avitaminosis which results from the increased use of the vitamins, especially nicotinic acid, by the body, owing either to local or general infection or to increased destruction of vitamins by bacterial toxins. Because of the fact that the good results of nicotinic acid therapy are not permanent for as long as focal infection remains, it is advisable to carry on the proper examinations of the patient in the course of nicotinic acid therapy in order to control properly the infection after administration of the substance.

J. A. M. A.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

R. P. MACKAY, M.D., *President, in the Chair*

Regular Meeting, Oct. 12, 1943

Localized Sweating as Part of a Localized Convulsive Seizure. DR. PAUL C. BUCY and DR. KARL H. PRIBRAM.

This article was published in full in the October 1943 issue of the ARCHIVES, page 456.

DISCUSSION

DR. ADRIEN VERBRUGGHEN: Could Dr. Bucy state the exact location of the areas involved? Was any attempt made to block the sympathetic fibers?

DR. L. J. MEDUNA: Did the sweating precede the movements, or did the movements occur first?

DR. SIGMUND KRUMHOLZ: There is now at Cook County Hospital a patient on Dr. Joseph Luhan's service who presents a clinical picture somewhat similar to the one described. This patient, a Negro in the 40's, has had epilepsy since the age of 3 years. However, beginning some time in September 1943, the family noticed that the grand mal attacks were accompanied by profuse perspiration over the whole right side of the face and body. The patient stated that he also has spells of dizziness without convulsions, during which he himself observes the unilateral sweating. This unusual phenomenon has been seen by some of the physicians at the hospital.

Physical examination revealed slight weakness of the right extremities, impairment of subcutaneous sensibility on the right side of the body and marked astereognosis of the right hand. The visual field of the right eye appeared to be limited, but the examination was gross and the results were not suitable for interpretation.

This unusual case points to the fact that localized sweating accompanying generalized epileptic seizures may be associated with a lesion in the parietal region. However, it is reasonable to assume that in this case the pathologic changes extend to the thalamus, the organ probably responsible for the localized sweating. May I ask Dr. Bucy whether, in his opinion, the localized perspiration in his case is symptomatic of a cortical lesion?

DR. PAUL C. BUCY: It is interesting to note the progress neurologists have made in the past ten or fifteen years. They have gradually come to realize that visceral and vegetative activities are not merely under the control of a system which is termed "autonomic," and which is independent of the central nervous system, but that all these activities, even sweating, are in variable degree subject to the influence of the cerebral cortex.

The case described by Dr. Krumholz is most interesting, but it would be difficult to draw sound physiologic conclusions when the nature and location of the pathologic lesion are unknown and the clinical manifestations of muscular weakness and sensory and visual abnormalities indicate widespread involvement.

I believe all would agree that in the case which Dr. Pribram and I have presented the localized unilateral convulsions of the face were indicative of cortical irritation. I see no reason to attribute the localized sweating which occurred simultaneously with the convulsions to any other cause. There was no evidence of thalamic irritation.

In answer to Dr. Meduna, as nearly as could be determined, the convulsion and the sweating occurred together. The muscular contractions may have preceded the sweating a little.

In reply to Dr. Verbrugghen, as there was no autopsy, the localization is not as detailed as one might desire. From the results of electrical excitation, we know that the tumor underlay the face area of the precentral gyrus. No effort was made to block the sympathetic nervous system.

In my experience continuous localized hyperhydrosis is due to peripheral, not to cerebral, disease. The most striking example of this type I have observed is that of a girl who suffered from such profuse, continuous sweating, localized to one side of the face and the shoulder, arm and axilla on that side, that one could literally catch the water in a cup as it dripped from her jaw. Examination disclosed spina bifida occulta of the lower cervical portion of the spine. The pathologic process responsible was probably a related myelodysplasia. The condition was completely relieved by a cervicothoracic sympathectomy. The sympathetic ganglia were normal on examination.

Physiology of Concussion. DR. A. EARL WALKER, DR. JERRY J. KOLLROS and DR. THEODORE J. CASE.

The experiments were performed on cats under anesthesia induced with pentobarbital sodium, or without general anesthesia after the cat had been prepared under vinethene and the incision desensitized with procaine hydrochloride.

Concussive effects were produced by hammer blows to the bare skull or by dropping weights of 14, 28, 50 and 80 Gm. from the height of 5 feet (152 cm.) onto a column of saline solution connected with the extradural space. The smallest weight failed to render the cat unconscious, while the largest weight usually had a fatal result. Several blows with the intermediate weights were required to produce death. A given weight was most effective when the blow struck the dura of the posterior fossa, somewhat less effective when it struck in the parietal region and least effective when it struck in the frontal region.

In the unanesthetized cats, and rarely in the anesthetized animals, the concussive blows usually produced a tonic fit of a few seconds' duration, followed by a clonic fit lasting up to thirty seconds. Such blows abolished respiration for from a few to ninety seconds and the corneal reflex for even longer.

The rise in intracranial pressure resulting from hammer blows and dropping of weights was measured by a Hamilton manometer. Generally the cannula on the side opposite the blow registered the highest pressure and that on the same side somewhat less, and with

frontal and occipital blows the cannula recording from the posterior fossa recorded the least pressure.

Hammer blows to the head produced in some cases increased pressure on the side of the blow and an initial decrease in pressure on the opposite side of the head. The latter phenomenon was considered an indication of the inertia of the semisolid brain as compared with the accelerated motion of the solid calvarium.

In the anesthetized preparation direct electrical stimulation of the motor cortex and of the hypothalamus (together with movement of the limbs and dilatation of the pupils) demonstrated the continued functioning of these regions after a concussive blow.

Pronounced changes appeared in the electroencephalogram immediately after concussion, such as reduction in the amplitude of waves, temporary abolition of activity in bursts during pentobarbital anesthesia and development of slow waves (1, 2 and 3 per second), as in cases of concussion in man.

When the animal was subjected to concussion without general anesthesia, an initial burst of irregular, rapid, spikelike activity of low amplitude was observed at times in the electroencephalogram. After thirty seconds this fast activity was replaced by slow waves.

In records from the occipital cortex, the "driving" of the cortex by intermittent photic stimulation was at first abolished by the blow; there was partial recovery of "driving" during the period of absence of the corneal reflex (i. e., the period of unconsciousness), and "driving" was frequently enhanced thereafter.

Strychninization of the cortex resulted in the appearance of large spikes in the electroencephalogram from the same side as that of the injection, as well as synchronous spikes from the opposite side. This cortical activity continued essentially unchanged after a concussion blow.

Concussion produced after two seconds a sharp rise in blood pressure, occasionally as much as 80 or 100 mm. of mercury above the preconcussion level. This rise is also obtained after section of one of the vagus nerves. If, then, either the central end of the cut vagus nerve or the ipsilateral carotid sinus nerve is stimulated, the blood pressure falls, and the pulse is slowed and made irregular. This demonstrates the continued ability of the cardioinhibitory mechanisms to function during the concussive state.

At each blow a large potential discharge occurs which unbalances the amplifiers of the electroencephalograph. To determine whether this discharge was produced by mechanical means or as a result of the actual discharge of nerve cells, a study was made, with utilization of a voltage divider in the electroencephalographic circuit. The effects of blows on the cortex of living and of dead animals were recorded. In general, the magnitude of the potential detected in the cortex of dead animals was of 1 millivolt or less, while that in the living preparations ranged from 3 to 40 millivolts. It is concluded that the discharge of potential is a biologic phenomenon indicative of the altered state of the nerve cell resulting from the cerebral trauma.

DISCUSSION

Dr. L. J. Pollock: How is the difference in pressure in different parts of the cranial cavity explained? Is it due to the existence of traveling waves of pressure? This is of interest and is of considerable importance in relation to concussion occurring from blast. When a person is immersed in a high pressure atmosphere, every portion of the body attains an equal pressure.

Dr. Paul Bucy: Because of the importance which some investigators have attached to the question of acceleration, I should like to ask whether concussion was produced with or without motion on the part of the head.

Dr. A. Earl Walker: Dr. Pollock's question regarding the different pressures obtained in different parts of the head is answered, I think, by the fact that the calvarium is not an entirely closed cavity. There are numerous openings through which blood passes, as well as openings into the orbits. Through these various openings the pressure is dissipated. This can readily be demonstrated by taking pressure readings from the carotid artery at the time of the blow and noting the increase at that moment. In cases of blast concussion there is little, or no, egress for the pressure wave.

Dr Bucy raises a much debated question. For the purpose of recording, the head was fixed in most of our experiments. On a number of occasions we permitted the head to be freely movable, and the results were not much different. We believe concussion is due to the "shaking up" of the intracranial contents, not to pure acceleration. When the head is freely movable, the cerebral commotion is likely to be more severe than when the head is fixed.

Cerebellar Ataxia Associated with Cerebral Signs.

Dr. Alex J. Arieff and Dr. Leo A. Kaplan.

We report 5 cases in which diseases that were not familial or hereditary produced a cumulation of signs and symptoms of dysarthria, cerebellar ataxia, intention tremor and involvement of the pyramidal tracts, and at times dementia and convulsions. The general similarity of the signs and symptoms led to discussion of the cases as a group. We present these cases not because they represent a clinical entity but merely because they illustrate the similar clinical manifestations produced by various etiologic factors. Unfortunately, pathologic material is not available. In 2 of the cases the symptoms were considered to be due to alcoholism; in 1 case, possibly to multiple sclerosis, and in the other 2 cases the cause could not be adequately classified.

REPORT OF CASES

Case 1.—W. C., a single white man aged 43, had been well until a year ago, when he became aware of shaking of the upper and lower extremities on the left side. This gradually increased, although it was present only on his attempting to carry out an act.

Examination revealed a pronounced intention tremor in all four extremities, most conspicuous on the left side. Speech was slightly explosive. There was no spasticity, although signs of disturbance of the pyramidal tract were present. Convulsive seizures had developed in the past three months. There was no evidence of psychic disturbance. Examination of the spinal fluid showed a colloidal gold curve characteristic of dementia paralytica. The encephalogram indicated moderate cortical atrophy. The patient is becoming progressively worse.

Case 2.—A white man aged 56 first noticed difficulty in speaking about fifteen years ago, his speech being described as thick and slurred. Inability to use his limbs then gradually developed, and he reeled like a drunken man. During the past two years he had convulsions.

Neurologic examination showed marked cerebellar ataxia in all four extremities; explosive, dysarthric

speech; hyperactive deep tendon reflexes; a suggestive Babinski sign on the right side; mental deterioration, and recurrent visual hallucinations. A pneumoencephalogram revealed moderate cortical atrophy. The patient has become progressively worse and is now practically bedridden.

CASE 3.—A man aged 59, an ex-pharmacist, had manifested difficulty in speaking, writing and walking during the past two years. He also had urinary incontinence. The essential neurologic signs were intention tremor; high-pitched, explosive speech; signs of involvement of the pyramidal tract bilaterally, most notable on the left, and mental deterioration. The course is slowly progressive.

CASE 4.—A white man aged 55, with a history of alcoholism for years, presented the outstanding symptoms of pronounced intention tremor in all four extremities; dysarthric, explosive speech, severe mental deterioration; hyperactive reflexes, and a suggestive Babinski sign bilaterally.

CASE 5.—E. A., a white man aged 35, had been well until a year ago, when he first noticed difficulty in walking. His gait was like that of a drunken man, and he was therefore frequently refused employment. He admitted having drunk to excess—at least a quart and a half (1.5 liters) of whisky a day—for nearly ten years.

Examination showed pronounced cerebellar ataxia in the lower extremities, with brisk reflexes throughout. Babinski and Rossolimo signs were present on the left side. An encephalogram revealed a moderate amount of air in the subarachnoid space. The course is progressive.

DISCUSSION

DR. LEO KAPLAN: The literature was meager with respect to the number of reported cases of chronic cerebellar ataxia due to alcoholism, and we appreciate the fact that many hesitate to accept the possibility of its occurrence. It is hard to understand why toxic infections and other vascular etiologic factors can produce cerebellar types of ataxia and alcohol cannot.

DR. R. P. MACKAY: The association of major convulsive seizures with multiple sclerosis is rare, but it does occur. I remember a patient who first had major seizures, and later multiple sclerosis.

R. P. MACKAY, M.D., *President, in the Chair*

Regular Meeting, Nov. 9, 1943

Paresis Following Corticospinal Section in the Monkey. DR. B. W. CANNON (by invitation).

In an investigation of the types of paresis following isolated lesions placed in the corticospinal system of the rhesus monkey, the effects of sections at two levels were studied—in the spinal cord and in the cerebral peduncle. In a series of 8 animals dorsolateral chordotomies were performed at either the cervical or the midthoracic level. The resulting paresis in the homolateral limbs was characterized by hypotonicity, by pendulous or hypoactive reflexes and by the absence of clonus. The paresis, which was more apparent in the lower extremity than in the upper one, affected the distal muscle groups to a greater degree than the proximal.

In a series of 6 monkeys the right or the left basis pedunculi was selectively interrupted. The paresis developing in the contralateral extremities subsequent to this corticospinal interruption was characterized by hypotonicity of all muscle groups except the extensors of the digits, by hyperactive deep reflexes and by the absence of clonus. The extended digits were the only sign of what might be considered hypertonicity.

Previously, Hines (*Bull. Johns Hopkins Hosp.* **60**: 313, 1937) reported the development of pure spastic paralysis, characterized by hypertonicity, hyperreflexia and clonus, subsequent to extirpation of cortical area 4-s. Later, Tower (*Brain* **63**:36, 1940) demonstrated that a syndrome consisting of hypotonic paresis, pendulous reflexes and absence of clonus followed interruption of the pyramids. Correlation of these results with those of the present investigation suggests that inhibitory pathways arising from area 4-s do not course entirely within the basis pedunculi. Fibers mediating the phenomenon of hypertonicity and those concerned with clonus, for the most part, have deviated from the corticospinal projection prior to reaching the cerebral peduncle; fibers concerned with hyperreflexia remain within the corticospinal projection while passing through the cerebral peduncle but deviate before reaching the pyramids.

DISCUSSION

DR. VICTOR E. GONDA: Until a few years ago the problems involved in these important investigations seemed fairly simple. There was the corticospinal and there was the spinomuscular neuron. Every one thought he knew exactly what happened if one set of these neurons was injured. It is still thought that the results of involvement of the spinomuscular neuron are understood. The problem becomes increasingly complicated the higher the level of the lesion in the nervous system; in the midbrain, and especially in the spinal cord, it is almost impossible to make circumscribed lesions involving the corticospinal tract alone.

Dr. Cannon proposed to deal with the nature of the paresis following section of the corticospinal tracts at different levels in the monkey. The assumption was that if the pyramidal tract was cut in the cervical or in the thoracic region of the spinal cord, the result would be hypotonicity and hyporeflexia. On the contrary, he observed hyperactive reflexes and hypertonicity, at least of the toes, when the pyramidal tract was sectioned in the midbrain. These observations are of great importance, inasmuch as it is conceivable that with the lesion in the midbrain the pyramidal fibers only were cut, whereas in the spinal cord it is practically impossible to cut the pyramids without cutting other tracts coming from or going to the brain.

In the drawings shown, according to my impression, the other tracts probably cut were the dorsal spinocerebral tract, the vestibulospinal tract and some of the extrapyramidal motor tracts. These facts must be considered in an evaluation of the resulting nature of paresis, and one cannot speak of paresis caused by section of the corticospinal tract alone. The elapsed time between the section and the examination also needs careful consideration.

Another factor must be taken into account in evaluation of the results of this important investigation. It was said that clinical neurologists were asked to evaluate the reflex responses in the partially paralyzed extremities of the monkeys. There are no definite data on even the physiologic reflexes in the extremities of the monkey. Many investigators state, and I think

correctly, that under normal circumstances the monkey shows no plantar responses. With a very strong stimulus one might notice some movement of the toes, but I think these are active movements connected with withdrawal of the extremities, and not reflex responses. Therefore, the first step is to solve this problem; then, and only then, can it be determined whether there are pathologic responses associated with lesions of the central nervous system.

I should like to suggest that it is important for one to become acquainted with the animals before the investigation is begun, so that they do not resist and struggle when handled.

DR. B. W. CANNON: Dr. Gonda's impression that the lesion inflicted by the dorsolateral chordotomy interrupted partially or completely paths in the spinal cord adjacent to the lateral corticospinal tract is quite correct. Yet the resulting paresis was essentially of the same type as was obtained by Tower after selective interruption of the corticospinal system at the level of the medulla by section of the pyramid. This similarity certainly minimizes the importance of the adjacent tracts of the dorsolateral column in modifying the paresis resulting from interruption of the corticospinal tract in the spinal cord. My associates and I have made a more complete report on the paresis following dorsolateral chordotomy (*J. Neurophysiol.* **6**:425, 1943).

The clinical neurologists' data on these animals were tabulated with respect to the presence or absence of the normal physiologic responses, such as the grasp reflex, the plantar response and the deep reflexes. For such responses no differences in opinion were expressed. There were, however, various differences of judgment as to the presence or absence of pathologic responses, not only the reflexes usually tested for in man but the responses described as significant in primates. For this reason, I have not included the pathologic reflexes in this report.

The animals were examined before operation and afterward, at intervals varying from the day following the section until as long as five months after operation in some cases.

Functional Organization of the Medial Surface of the Primate Cortex. DR. W. S. MCCULLOCH and (by invitation) DR. GERHARDT VON BONIN.

By local strychninization and recording of the induced alterations of electrical activity, the following areas on or near the gyrus cinguli of the macaque and the chimpanzee were identified. Area 24, in the anterior part of the gyrus, is a suppressor area. It sends projection fibers to the nucleus caudatus. Area 23, in the posterior and superior part, sends impulses to the preoccipital and parastriate areas and projection fibers to the anterior nucleus of the thalamus in the macaque. Area 29, close to the splenium of the corpus callosum, was not observed to have other cortical connections but also sends projection pathways to the anterior nucleus of the thalamus in the macaque. Along the sulcus cinguli there is a "cingular belt," homologous with areas 32 and 31, which receives connections from all known suppressor areas of the cortex (areas 24-s, 8-s, 2-s and 19-s) but does not send projection tracts to them. Area 32 has commissural connections, but none has been demonstrated for area 31.

Areas on the medial surface of the frontal lobe of the chimpanzee which may correspond to Brodmann's areas 10, 11 and 12 were identified and their firing characteristics determined. These were not identified in the macaque.

DISCUSSION

DR. GERHARDT VON BONIN: I might throw some light on the differentiation of areas 31 and 32. They behave as one area in affording a connection between the parietal and the frontal lobe. They differ histologically, however. Area 32, in front, is agranular; it is hard to differentiate from area 6. Area 31 is granular and is of the parietal type. Area 31 has callosal connections; area 32 does not. Area 23 sends projection fibers, as has just been stated, into areas 19 and 18, which are definite visual areas. What they do and what their function is I do not know.

Dr. McCulloch and I carried out some experiments in connection with the thalamic nuclei. We cut the corpus callosum and laid bare the thalamus and strychninized the various areas. Strychninization of areas 23 and 29 gave rise to spikes in potentials from the anterior nucleus of the thalamus.

DR. A. EARL WALKER: Dr. Bailey has asked about the fibers from area 4-s to the callosal gyrus. In a chimpanzee in which area 4-s had been removed I was able to trace degenerated myelinated fibers down to the gyrus callosomarginalis. I observed no evidence of degenerated fibers passing down to the thalamus.

Some of the results of the physiologic studies presented by the authors add confirmation to previous anatomic observations. The method of study which Dr. McCulloch uses is so much simpler and less time consuming than the anatomic approach that many anatomists are loath to give it full credence. When anatomic and physiologic methods produce similar results, it is gratifying.

Diffuse Leukoencephalopathy Without Sclerosis. DR. HERMAN JOSEPHY, Lincoln, Ill. (by invitation) and DR. BEN W. LICHTENSTEIN.

This paper was published in the November 1943 issue of the ARCHIVES, page 575.

DISCUSSION

DR. HERMAN JOSEPHY, Lincoln, Ill.: The old concept of diffuse sclerosis, which included under the same head degenerative, inflammatory and even blastomatous demyelinating processes, was based on the results of staining the myelin sheaths, a method which, however, cannot give evidence of the true nature of the underlying process. Undoubtedly, neither the inflammatory nor the blastomatous form has any relation to the degenerative form. It would be a mistake, however, to think of the degenerative type as a morbid entity. Very likely the pathogenesis is not the same in all cases of this form.

The first case we report shows, in an interesting way, the limitation of the histologic methods. I cannot see how the peculiar liquefaction can be explained on the basis of any microscopic evidence. Such a problem, probably, can be approached only by biochemical or colloid chemical methods. As to the clinical aspect of our cases, both are examples of the rare situation in which a head which is of hydrocephalic type is not associated with a hydrocephalic brain. Unfortunately, no spinal puncture, not to speak of an encephalographic examination was done.

DR. WILLIAM F. WINDLE: I got the impression that the cortex was relatively normal. I wonder whether

the cortex over the areas of complete liquefaction of white matter could be even relatively normal. It would be constructive if a little more were known about the autopsy in this case—how soon after death the brain was obtained, and how it was treated.

DR. HERMAN JOSEPHY, Lincoln, Ill.: The autopsy was performed soon after death, and portions of the brain were fixed immediately in a dilute solution of formaldehyde and in alcohol. I am sure there was no postmortem decomposition.

DR. R. P. MACKAY: If postmortem changes had caused this profound degeneration of the white matter, why did the cortex not show degeneration in the same degree? The absence of wallerian degeneration in the corticospinal and other descending pathways is the rule in the diffuse scleroses, and hence is not surprising in this case. It is important to recognize that these conditions are not so rare as one might suppose.

I have under observation at present a man aged 49 in whom steadily progressive signs of cerebral disease suggested the existence of a tumor of the brain. Pneumoencephalographic studies revealed diffuse dilatation of the ventricular system. One is forced to assume widespread degeneration of the white matter. Careful pathologic study like the one just reported, if done more often, would sharpen clinical appreciation of these conditions.

DR. BEN W. LICHTENSTEIN: The degeneration of the white substance shown in the lantern slide is a combination of true degeneration and artefact. It will be recalled that some white substance ran out when the brain was sectioned. Sections through the pyramidal tract, however, did show degeneration, indicating a primary disease process. The cortex presented extensive atrophy and shrinkage of the nerve cells. This was probably the result of the subcortical disease process. On the whole, the cortex was well preserved, as compared with the degenerated centrum semiovale.

PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President, in the Chair*

Regular Meeting, Nov. 12, 1943

History of Psychiatry in Philadelphia. DR. EARL D. BOND.

Newer Applications of Narcosis Therapy in War Psychiatry. DR. HAROLD D. PALMER.

Narcosis therapy has been much neglected in psychiatric practice. It is by no means a new treatment, since it was used more than fifty years ago in European psychiatric centers. In 1929 Dr. A. L. Paine and I began an investigation of the effects of narcosis induced with sodium amytal in patients with manic-depressive psychoses, schizophrenia, involutional melancholia and psychoneuroses (*Am. J. Psychiat.* **89:** 143-165, 1932). The increased accessibility and release of repressed material under the influence of the hypnotic drug seemed to be its most striking effect. From 1929 until 1936 my associates and I treated more than 100 patients at the Pennsylvania Hospital, and Dr. F. J. Braceland and I reported the results (*Am. J. Psychiat.* **94:**37-54, 1937).

The narcosis treatment may be prolonged or partial. In prolonged narcosis, applicable especially to treatment of acute psychotic episodes and violent, disturbed psychotic states, sodium amytal, by intravenous and by rectal administration, is employed in an effort to keep the patient in a state of somnolence from three to twenty-one days. The recent literature on war psychoses indicates that the results have been satisfactory, especially in treatment of the psychoses associated with exhaustion states, as indicated by the reports in *War Medicine*, the British medical periodicals and other current journals. Partial narcosis has been used with great success in the treatment of hysterical amnesia, aphonia and paralyses. My associates and I have limited our use of partial narcosis to acute anxiety panic reactions, hysterical amnesia and other manifestations of the neuroses. In treatment of severe obsessive-compulsive states, inaccessible to psychotherapy over a period of years, we have obtained remarkable results with this method of repeated light anesthesia induced with sodium amytal. Other uses for partial narcosis described in the literature are in treatment of drug addiction and as a prognostic test in selection of prospective patients for insulin and electric shock therapy. Several authors have stated that if partial narcosis produces euphoria, emotional relaxation and transient freedom from all psychotic symptoms, good results from shock therapy may be anticipated. If, on the other hand, these changes do not occur with partial narcosis, the results of shock therapy will be poor.

In the management of war neuroses partial narcosis has achieved its most spectacular success. Utilizing what is known of the passive receptivity and the release phenomena associated with narcosis therapy, psychiatrists in the armed forces have achieved a high percentage of recoveries from many types of neuroses, especially the acute combat neuroses. Pentothal sodium and sodium amytal, administered intravenously, have the effect of facilitating rapport and breaking down resistance, allaying acute, violent panic states and making accessible conflict material formerly deeply repressed. In the narcosis state active interference by suggestion is accomplished. Several terms have been applied to this technic, such as pharmacohypnosis (Reitman), narcoanalysis (Horsley), drug analytic method (Jelliffe) and narcosynthesis (Tureen, Hanson and Grinker). In a recent release by the Office of War Information, the late Colonel Halloran cited the recovery and return to active combat duty within two to five days of from 50 to 70 per cent of all men with acute combat neuroses. It has been found that many of the men with acute war neuroses have abnormal electroencephalograms but that after narcosis they return to normal. The reintegration, therefore, is on a physiologic as well as a psychologic basis. This war has taught that the neuroses of combat result from prolonged, and not sudden, strain and stress and that the prognosis is directly related to the promptness of treatment after the development of the neurotic disabilities. If one could attack the earliest manifestations of ego disintegration in civilian cases, perhaps many of the fixed neuroses could be avoided.

DISCUSSION

DR. J. C. YASKIN: I have had a few interesting experiences with narcosis therapy. Several years ago I treated a patient with spasmodic torticollis by this means, with satisfactory results (*J. Nerv. & Ment.*

Dis. **81**:299 [March] 1935). I used the method for another patient with spasmodic torticollis, with considerable improvement but not complete recovery.

I found induction of narcosis with sodium amytal useful with acute anxiety states of the psychoneurotic type. Two or three days of continuous sleep prepares the patient for other therapeutic approaches.

Within the last two years I have had interesting experiences with sodium amytal narcosis in treatment of neurogenic dermatitis. A woman had had severe recurrent dermatitis for several years. After three weeks of this therapy she had completely recovered.

A disturbing feature of treatment with sodium amytal narcosis is the rise in temperature which sometimes occurs. This proved particularly disquieting in a case of gallstone colic in which severe panic had developed, so that the operation could not be performed. For the acute anxiety state the patient was subjected to sodium amytal narcosis, which was followed by a rather severe febrile reaction. I should like Dr. Palmer to discuss this complication and other disturbing features of narcosis therapy.

Dr. Harold D. Palmer: I am much interested in hearing Dr. Yaskin report notable improvement in patients with dermatitis during prolonged narcosis therapy. In a number of our patients acneform eruptions of the skin, severe colitis and other conditions disappeared during prolonged narcosis. Improvement in general somatic health was the rule. The question of fever arising during the course of treatment has been discussed at length by some British psychiatrists who used somnifene (diethyldiallylbarbiturate of diethylamine) and other drugs, but in our patients fever occurred in only 15 of 115 prolonged treatments with sodium amytal narcosis, and in none of these was the increase in temperature sufficient to warrant the termination of treatment. When my associates and I were using phenobarbital in 1929 and 1930, fever was a troublesome complication. It is our belief that fever occurring in the course of sodium amytal narcosis is the result of infection and is not due, as some investigators think, to a disturbance of the thalamic centers produced by the drug. In cases in which the systolic blood pressure drops below 70 mm. of mercury there may be suppression of urinary secretion, and it has occasionally been necessary to give ephedrine or picrotoxin to restore the blood pressure to more normal levels.

Clinical and Biochemical Observations on Intravenous Administration of Insulin in Shock Therapy. Dr. Eugene Revitch; read by Dr. Matthew T. Moore.

A number of articles have appeared recently (1940 to 1942) concerning the intravenous administration of insulin in shock therapy.

In order to determine the advisability of using this method at the Philadelphia Psychiatric Hospital, 11 patients were studied. The purpose of the investigation was to learn whether the method would save time and insulin; the nature of the complications, if they occur; the difference in the blood sugar curves for subcutaneous and for intravenous administration of insulin, and the relation of the method of administration and the dose of insulin to the hypoglycemic reaction.

With the intravenous method there was gain of as much as two hours and forty-five minutes in the time required for the production of coma, or an average of sixty-eight minutes over the time required by the subcutaneous method. For sweating there was a gain of forty-five to ninety minutes; for stupor, a gain of forty-five to ninety minutes, and for twitchings, when they occurred, a gain of thirty to one hundred and fifty minutes. The average time for the development of coma with the intravenous method was eighty-five minutes.

The insulin dose required for production of coma in 25 patients treated by subcutaneous injection was 110 to 400 units, the average dose being 230 units. In 10 of the patients treated intravenously, the production of coma or stupor required the same doses of insulin as those used by the subcutaneous route (110 to 510 units). These results show that patients can be treated by the intravenous method with the same doses and at the same tempo as by the subcutaneous method.

Of 11 patients, 1 had abdominal pain; 1, a bigeminal pulse; 2, allergic reactions; 2, epileptoid convulsions and tonic spasms, and 2, secondary shock, and 3 showed no untoward reactions. In general, we found a higher incidence of secondary shock, tonic spasms and allergic reactions with the intravenous method.

Comparison of the curve for the subcutaneous method with that for the intravenous method showed that with both methods the curve fell rapidly the first half-hour and that it reached lower levels with the intravenous method than with the subcutaneous method. After the first hour both curves had a tendency to rise, but the curve for the intravenous method rose higher and more rapidly. Comparison of the curves for the two methods produced with different amounts of insulin revealed that in several instances the levels of the blood sugar for the same patient were the same the first half-hour with the use of widely different doses. In general, large amounts had a tendency to depress the restoration line more than the assimilation line. At the lowest levels of the curve, when the sugar of the blood dropped to 20 or 25 mg. per hundred cubic centimeters, the patients felt comfortable, and only later, during the restoration period of the curve, did they show the so-called hypoglycemic reactions. The patients did not become comatose with low levels of the blood sugar produced by small amounts of insulin. They showed pronounced reactions, however, with larger doses, although there was essentially no great difference in the level of the blood sugar. Curves for the level of the blood sugar produced by the intravenous administration of insulin showed a greater fall in the first half-hour and a more rapid rise in the restoration curve. The curve for the blood sugar was depressed to a greater degree with larger doses of insulin. In several instances the assimilation line reached the same level with widely different amounts of insulin, but the restoration line followed the rule that larger amounts of insulin depress the curve more than smaller amounts. Hypoglycemic reactions lagged behind the changes in the blood sugar, an indication that hypoglycemia alone was not responsible for the clinical reactions. In my opinion, coma is due to a direct action of insulin on the metabolism of the brain cells.

DISCUSSION

Dr. H. H. Herskovitz, Norristown, Pa.: This is a comprehensive paper on the intravenous administration of insulin. At Norristown State Hospital we found a saving in time of half an hour by the use of this method.

Dr. N. W. Winkelman: The work reported here really started as the result of the present war "short-

ages." Because we were short of help at the hospital, we tried to devise a "short cut" method of giving insulin therapy. In view of the advantages claimed by some workers for the intravenous use of insulin, we decided to see whether the method would solve our problems. We found that we could save but little time. In the course of this study, however, we made some interesting clinical and laboratory observations, which Dr. Revitch has recorded.

DR. MATTHEW T. MOORE: A sugar content of the blood of below 20 or 15 mg. per hundred cubic centimeters does not represent the true amount of dextrose in the blood, since other substances are present which affect the reading; thus the value for dextrose is actually lower than the report indicates. Aside from the possibility of the saving of time and material by intravenous administration of insulin, my associates and I have been evaluating the use of insulin in the treatment of various psychoses as compared with that of other methods, and have been interested in its mode of action. Does insulin act as a sort of chemical knife, producing predilective changes in the frontal lobe, as would frontal leukotomy, or does it affect the neurons generally? Again, we have been concerned with the possible damage insulin may produce in the brains of patients who might otherwise have a remission in the ordinary course of events. We believe that in large doses insulin acts as a direct poison to the ganglion cells, and we use the substance, therefore, with only selected groups of schizophrenic patients for whom statistical and clinical experience indicates it to be of some value.

Psychic Death: Report of a Possible Case. DR. MARY JANE WALTERS.

An American-born woman of Italian descent, whose mother died at the age of 42 in a mental disease hospital after an induced abortion, felt that she would die like her mother at the same age, and she did achieve death in a mental disease hospital in her forty-second year. Yet she did not commit overt suicide, suffer any known accident or succumb to any recognized organic disease. She had been physically healthy all her life, and repeated examination and routine laboratory tests in both the hospitals in which she spent eleven months of her last two years revealed nothing significant up to within a few hours of the death.

The patient had resented so greatly the intrusion into the family of a stepmother that she became hostile toward her father, feeling he had caused her mother's death. Her hostility increased when her own husband did not meet her expectations socially and financially. Her whole married life was marked by dissatisfaction. She did not want a "big family, like most Italian women." She had several abortions. Finally, when nearly 40, she missed a period and took "pills" to produce an abortion. She then became so panicky for fear she was poisoned that commitment to an institution was necessary. The diagnosis was paranoid schizophrenia. She expressed repeatedly the idea that she would have to follow the family pattern and die like her mother (and aunt), at the age of 42. She improved sufficiently to be at home for three months; then suddenly, after a visit from her father, she again became acutely disturbed and hallucinated. On readmission to the institution she tried to jump out of the window, to "die like my mother."

Her last two weeks were marked by extreme excitement and fearfulness. However, she took food and fluids fairly well and showed no evidence of poisoning or infection. Her temperature, pulse and respirations were normal until the last eighteen hours of her life. Then her temperature became subnormal; her pulse grew gradually weaker, and her respiratory rate increased to about 48 a minute. She lapsed into coma on the anniversary of the mother's death and died the day after, in the seventh month of her forty-second year. The nitrogen of the blood eight hours before death was 70 mg. per hundred cubic centimeters. Permission for autopsy was refused. While certain constitutional factors were recognized, it was felt that the most notable feature of the case was the patient's identification with her mother. It is probable that the cause of death was renal failure brought about by acute emotionalism.

DISCUSSION

DR. H. H. HERSKOVITZ, Norristown, Pa.: Exhaustion is frequently a cause of death in cases of mental disease. We are convinced this death was not due to exhaustion. The patient was sure she was going to die by her forty-second year, and she did, being in coma on the anniversary of her mother's death and dying one day later. I think psychiatrists recognize the possibility of psychic death but few cases are recorded.

DR. EARL D. BOND: At the Danvers State Hospital, in 1910, a man was admitted in a panic, of three days' duration. He paid little attention to the hospital but kept staring out of the window at people, who, he said, were coming to lynch him. Finally, with the words, "They are coming now," he fell over dead. Autopsy showed that the organs were in amazingly good condition; no lesions were observed anywhere.

DR. N. W. WINKELMAN: The question of a psychic death brings up many interesting and debatable points. It is well known that occasionally a complete autopsy is done without its revealing the actual and immediate cause of death. In cases in which death has been instantaneous, as from coronary thrombosis, it may not be possible, except by careful dissection, to find the locus and nature of the lesion.

In the case presented this evening I must confess that the terminal picture does not look like that of a purely psychic disturbance. The fact that the patient predicted her death on a certain day is not unusual, and it is mathematically possible for a patient to hit occasionally on the exact time of death. I have seen patients who have predicted their deaths year in and year out for the last twenty-five years and are still living.

I am not forgetting, nor am I eliminating, the effect of the emotions on the heart and the blood pressure, but I believe that the problem in this case is one in which a basic organic change was present but in which the emotional reaction seemed more important than it really was.

DR. MATTHEW T. MOORE: I think it is possible to correlate psychic disturbances with organic mechanisms. In discussing a case such as that presented here, it may be wondered whether one is treading in the tenuous domain of mysticism. Frazier, in his "The Golden Bough," cited several instances of what was undoubtedly "psychic death," in which the tribal belief of the certain visitation of death on the failure of observance

of special taboos was so deeply conditioned that death did ensue when the victim realized he had broken one. Some years ago I treated a woman who had lost all the members of her family and who felt completely lost in the world. She was depressed, expressed the belief that she had a serious heart condition and stated that she would die within twenty-four hours. Physical examination showed no organic defects of any kind. The following morning she was found dead. Post-mortem examination showed no evidence of ingested poison or of trauma.

It is generally accepted that continued emotional stress can produce functional changes eventuating in myocardial changes. Shock or syncope can be induced acutely by intense emotional stress. The author stated that she believed the changes were due to more or less continuous sympathetic bombardment on the organism, a concept which fits in with the organic aspect of which Dr. Winkelman spoke. The "psychic death," therefore, was truly of organic nature, produced by a conditional functional derangement secondary to an acute or long persistent emotional stimulus, and was not due to a mystical death wish.

Book Reviews

Psychosomatic Diagnosis. By Flanders Dunbar, M.D., Med. Sc. D., Ph.D. Price $7.50. Pp. 741. New York. Paul B. Hoeber, Inc., 1943.

This is a book by one of the pioneers in psychosomatic medicine. For years the author and her colleagues have followed and studied patients with somatic illnesses and have elicited pertinent psychologic data which they feel have enabled them better to understand the picture of the patient's illness, with facilitation of more judicious diagnostic and therapeutic procedures.

The book is devoted to a description of experiences with 1,600 patients, many of whom were observed for as long as twelve years. The syndromes included in this study are hypertensive cardiovascular disease; coronary occlusion; rheumatic fever, with and without cardiac and arthritic involvement; diabetes; anginal syndrome, and cardiac arrhythmias. In an attempt to obtain suitable control patients, the author decided to utilize patients with fracture but soon found that there were psychologic aspects to their problems also. She therefore included them in this series, having to be satisfied with contrasting the various pictures.

Methods of psychosomatic study and examination are described, with numerous case illustrations. The author then goes on to a statistical analysis of the material in terms of such factors as age, sex, occupation, education and previous illnesses. Out of this analysis has grown what is the important contribution of the study, and, at the same time, probably the most controversial part of it—the profile. The author and her colleagues found that each syndrome has its specific personality profile, in pronounced contrast to others. Although individual factors in the profile may be the same in different illnesses, the over-all sum of these factors builds a personality picture quite different for the various illnesses. The features enabling one to construct a profile may be summerized as follows:

1. Family history. It is more significant to obtain the history of exposure to illness than it is to ascertain the existence of such illness in various members of the family.

2. Personal data, such as marriage, divorce and number of children.

3. Health record.

4. Injuries.

5. General adjustment, including education, occupation, income and sexual and social adjustment.

6. Characteristic behavior pattern—the patient's handling of his environment and problems arising in his relationship to other people.

7. History of neurotic traits.

8. Particular interests and addictions, such as alcoholism.

9. Life situation immediately prior to onset of illness.

10. Reaction to illness.

11. Area of focal conflict and characteristic reaction.

All the syndromes are studied with these, and many other, features in mind, and there are numerous illustrative case histories. For example, in contrasting the area of focal conflict and characteristic reaction of the patient with fracture and the corresponding features of the patient with hypertension, the author states with respect to the latter: "Their basic conflict is between authority identification and their need to be taken care of—active-passive drives. They are constantly ambivalent and hence experience obsessive difficulty in making decisions or determining a course of action. This is often verbalized in a preoccupation with intellectual pros and cons. They tend to court much more responsibility than they are able to carry." Of the former she says: "They seem to be striving toward integration and autonomy outside of the authoritarian heirachy. They show a tendency to make up their minds definitely and quickly, to focus upon immediate values and they display little interest in intellectual values and verbalizations."

Out of these evaluations of personality arise many therapeutic implications, which are presented and discussed, with illustrative cases. Although here and there attempts are made to establish etiologic correlations between the personality profile and the somatic illness, the author generally avoids drawing any major conclusions.

Undoubtedly this work will receive much criticism. For instance, the book is not well written and is at times confusing. This defect may be due to the detailed statistical elaborations, which lend the study its scientific background. However, a comprehensive bibliography of the literature on psychosomatic disease offers an opportunity for further reading and clarification. The absence of a satisfactory control group of patients may lead many observers to question the validity of the study. In the main, however, these criticisms do not detract from the fact that this work represents a valuable preliminary contribution to psychosomatic medicine and is therefore a "must" to persons interested in that field.